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THE PHYSIOLOGY OF REPRODUCTION

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TO

WALTER HEAPE, Esq., M.A., F.R.S.

PREFACE TO SECOND EDITION

In preparing a new edition of "The Physiology of Reproduction" (the first edition having been for some time out of print) an attempt has been made to bring the book up to date, and much new matter has been added. Dr. Cramer has enlarged and partly rewritten his chapter on the "Biochemistry of the Sexual Organs," besides performing a similar service in respect of Dr. Lochhead's chapter on the "Changes in the Maternal Organism During Pregnancy," to which many important additions have been made; Dr. Lochhead, unfortunately, owing to his professional duties at Gibraltar, having been unable to revise his former contributions. The chapter on "Fœtal Nutrition and the Physiology of the Placenta," by the latter author, has been reprinted practically as it originally stood, excepting for certain slight additions, chiefly in the form of footnotes, for which I am responsible. It is believed, however, that the chapter is in no sense out of date, since the quantity of original work done in this field during the last decade has been relatively small. Dr. Shearer has added to the value of the chapter on "Fertilisation" by including a description of the Oxidation Processes Occurring in the Egg at and after Fertilisation, as well as an account of Child's work on the Life Cycle; he has also given me the benefit of his wide knowledge of the literature in the revision of other parts of the book. In addition to Dr. Cramer and Dr. Shearer, I wish also especially to thank my colleague, Mr. John Hammond, for his valuable and ready help in the preparation of this edition. Besides affording me the advantage of his extensive knowledge and experience, he has placed at my disposal his numerous notes relating to different branches of Generative Physiology.

I have pleasure in expressing my obligations to those authors, editors, and publishers who have permitted me to reproduce illustrations from their respective works; in particular I must mention Professor E. Steinach, of Vienna; Dr. A. Pézard, of Paris; and Dr. H. D. Goodale, of Amherst, Mass., U.S.A. I am indebted also to the following for help in revising the proofs, for supplying me with important references, or for assistance in other ways:—Professor J. T. Wilson, of Cambridge; Professor C. G. Seligman, of London; Dr. W. Blair Bell, of Liverpool; Mr. H. M. Fox, of Gonville and Caius College; Dr. A. C. Haddon, of Christ's College; Mr. K. J. J. Mackenzie, of Christ's College; Mr. L. F. Messel, of Magdalene College; Mr. M. S. Pease, of Trinity College; Dr. R. H. Rastall, of Christ's College; Mr. H. G. Sanders, of St. John's College; Mr. J. T. Saunders, of Christ's College; Dr. J. M. Duncan Scott, of Edinburgh; and Mr. R. Weatherall, of Christ's College. To Mr. Alan S. Parkes, of Christ's College, I am under a special obligation for the great trouble he has taken in preparing the indices and reading the final proof sheets.

I wish further to express my gratitude to Messrs. Longmans, Green, & Co. for having met my wishes in all possible respects in matters connected with publication.

The introduction to the first edition is reprinted as it originally stood, except for a few necessary corrections.

It is now more than twenty-two years since, in association with Professor Cossar Ewart and Professor (now Sir Edward) Sharpey Schafer at Edinburgh, I began the series of investigations on the œstrous cycle from which the present work has grown, and I take this further opportunity of thanking all who helped me in those early days. Particularly I must mention Lord Carmichael of Skirling, without whose generosity it would, in the absence of a regular endowment, have been impossible to have conducted researches on so extensive a scale. Since 1908 the work has been continued at Cambridge, and I wish also to thank my colleagues in the schools of Agriculture and Physiology, as well as the Master and Fellows of my own college, for all they have done to make that work possible, and for their never-failing encouragement during the past fourteen years.

F. H. A. MARSHALL.

CHRIST'S COLLEGE, CAMBRIDGE,
August 1922.

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THE PHYSIOLOGY OF REPRODUCTION

INTRODUCTION

SINCE the time when physiology first became an organised science many volumes have been written on the digestive, excretory, nervous, and other systems, but until recently no attempt has been made to supply those interested in the reproductive processes with a comprehensive treatise dealing with this branch of knowledge. Indeed, in many text-books on physiology now commonly in use either the section devoted to the reproductive organs is restricted to a few final pages seldom free from error, or else the subject is entirely omitted. Yet generative physiology forms the basis of gynæcological science, and must ever bear a close relation to the study of animal breeding. In writing the present volume, therefore, I have been actuated by the desire to supply what appeared to me to be a real deficiency; and in doing so I have attempted, however inadequately, to co-ordinate or give a connected account of various groups of ascertained facts which hitherto had not been brought into relation. For this purpose I have had occasion to refer to many books and memoirs dealing with subjects that at first sight might have been supposed to differ widely. Thus, works on zoology and anatomy, obstetrics and gynæcology, physiology and agriculture, anthropology and statistics, have been consulted for such observations and records as seemed to have a bearing on the problems of reproduction.

My sources of information are duly acknowledged in the footnotes, but I am glad to take this opportunity of mentioning the following works from which I have obtained special help: "The Evolution of Sex," by Professors Geddes and Thomson; "Obstetrics," by Professor Whitridge Williams; the sections on the male and female reproductive organs, by Professor Nagel and Dr. Sellheim, in Professor Nagel's "Handbuch der Physiologie des Menschen"; "Experimental Zoology," by Professor T. H. Morgan; and the writings of Mr. Walter Heape.

The present volume is addressed primarily to the trained biologist, but it is hoped that it may be of interest also to medical men engaged in gynæcological practice, as well as to veterinarians and breeders of animals. As a general rule, I have confined myself to the physiology of generation among the higher forms, and more particularly the Mammalia, but I have not hesitated to discuss the reproductive processes in the Invertebrata in cases where they seemed likely to elucidate the more complex phenomena displayed by the higher animals. The all-important questions of heredity and variation, although intimately connected with the study of reproduction, are not here touched upon, excepting for the merest reference, since these subjects have been dealt with in various recent works, and any attempt to include them would have involved the writing of a far larger book. Similarly, the subject matter of cytology, as treated in such works as Professor Wilson's volume on the cell or the recent works by Professor Agar and the late Professor Doncaster, is also for the most part excluded.

It may be objected that for a book on physiology much space is devoted to the morphological side of the subject. This has been done purposely, since it seemed impossible to deal adequately with the physiological significance of the various sexual processes without describing the anatomical changes which these processes involve.

In preparing this work I have been assisted by many friends. I have been fortunate in securing the co-operation of Dr. William Cramer and Dr. James Lochhead, of the University of Edinburgh. Dr. Cramer has contributed the section on the biochemistry of the sexual organs, while Dr. Lochhead has written the chapters on fœtal nutrition and the metabolism of pregnancy, a labour of no inconsiderable magnitude in view of the complexity of the subject. I take this opportunity of recording my indebtedness to Mr. Walter Heape, through whose influence I was first led to realise the importance of generative physiology both in its purely scientific and in its practical aspects. I am under no light obligation to Professor Sir Edward Sharpey Schafer for valuable and ready help at all stages in the preparation of this volume. Not only did he look through the original manuscript of the chapter on "The Testicle and Ovary as Organs of Internal Secretion," but he gave also much helpful advice and criticism on various points connected with publication. Indeed, it is not too much to say that had it not been for him, the book would scarcely have been written. Sir Hugh K. Anderson, Master of Gonville and Caius College, and Professor Sutherland Simpson have read the manuscript or first proofs of the chapter dealing with "The Accessory Male Organs." The late Mr. E. S. Carmichael, of the Royal Infirmary, Edinburgh, read the section dealing with parturition. Professor J. H. Ashworth looked through the chapter on "Fertilisation" in the first edition; and Professor F. G. Hopkins did the same for Dr. Cramer's biochemical chapter. Sir H. Anderson and Professor Ashworth have also given me the benefit of their special knowledge in other parts of the work. To all these I am under obligations. I wish also to tender my thanks to those authors and publishers who have kindly allowed me to reproduce illustrations from their respective works, as well as to record my indebtedness to the following, who have been of service by giving me information, important references, or assistance in other ways:—Dr. Nelson Annandale, Superintendent of the Indian Museum, Calcutta; Dr. W. Blair Bell, of Liverpool; Dr. Eagle Clarke, lately Superintendent of the Scottish National Museum; Professor J. C. Ewart, of the University of Edinburgh; Professor J. P. Hill, of University College, London; Dr. A. C. Haddon, of Christ's College; Professor W. A. Jolly, of the University of Cape Town; Dr. Janet E. Lane-Claypon, of London; Mr. D. G. Lillie, of St. John's College; Mr. K. J. J. Mackenzie, of Christ's College; Mr. F. A. Potts, of Trinity Hall; Professor C. G. Seligman, of London; and Sir Arthur E. Shipley, Master of Christ's College. Lastly, I wish to acknowledge the assistance of Dr. C. H. Crawshaw, of Christ's College, in the correction of the first proofs, as well as to express my obligations to Mrs. Hingston Quiggin for the willing labour she expended in preparing the index and finally revising the text of the first edition, and to Mr. Richard Muir for the skilful manner in which he executed those drawings which were new.

CHAPTER I

THE BREEDING SEASON

"To everything there is a season, and a time to every purpose under the heaven."—*Ecclesiastes* iii. 1.

"It is well known that almost all animals, except man, have a stated season for the propagation of their species. Thus the female cat receives the male in September, January, and May. The she-wolf and fox in January; the doe in September and October. The spring and summer are the seasons appointed for the amours of birds, and many species of fishes. The immense tribe of insects have likewise a determinate time for perpetuating their kind; this is the fine part of the year, and particularly in autumn and spring. The last-mentioned class of beings is subject to a variation that is not observed in the others. Unusual warmth or cold does not retard or forward the conjunction of birds or quadrupeds; but a late spring delays the amours of insects, and an early one forwards them. Thus it is observed that, in the same country, the insects on the mountains are later than in the plains."

The foregoing quotation from Spallanzani's "Dissertations,"[1] although not strictly accurate in all its statements, contains a clear recognition of two fundamental facts which indeed have been realised from the earliest times; first, that the periods of reproductive activity among the great majority of animals (not to mention plants) occur rhythmically, the rhythm having a close connection with the changes of the seasons; and secondly, that the reproductive rhythm is liable, to a greater or less extent, to be disturbed or altered by climatic or other environmental influences. And while there may be a basis of truth for the statement that the periodicity of the breeding season in the higher animals is less liable to modification than is the case with certain of the lower forms of life, there is abundant evidence that among the former no less than among insects the sexual functions are affected by external conditions and food supply.

Darwin remarks that any sort of change in the habits of life of an animal, provided it be great enough, tends in some way to affect the powers of reproduction. "The result depends more on the constitution of the species than on the nature of the change; for certain whole groups are affected more than others; but exceptions always occur, for some species in the most fertile groups refuse to breed, and some in the most sterile groups breed freely." "Sufficient evidence has now been advanced to prove that animals when first confined are eminently liable to suffer in their reproductive systems. We feel at first naturally inclined to attribute the result to loss of health, or at least to loss of vigour; but this view can hardly be admitted when we reflect how healthy, long-lived, and vigorous many animals are under captivity, such as parrots and hawks when used for hunting, chetahs when used for hunting, and elephants. The reproductive organs themselves are not diseased; and the diseases, from which animals in menageries usually perish, are not those which in any way affect their fertility."[1]

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[1] Spallanzani, *Dissertations relative to the Natural History of Animals and Vegetables.* Translated from the Italian, vol. ii., London, 1784.

It would seem probable that failure to breed among animals in a strange environment is due not, as has been suggested, to any toxic influence on the organs of generation, but to the same causes as those which restrict breeding in a state of nature to certain particular seasons, and that the sexual instinct can only be called into play in response to definite stimuli, the existence of which depends to a large extent upon appropriate seasonal and climatic changes.[2]

There are at present no sufficient data for a comparative account of the physiology of breeding among the lower animals; and in the present chapter, which is preliminary in character, I shall content myself with stating a few general facts about the breeding season, giving illustrations, taken from various groups of Vertebrates and Invertebrates, of its seasonal recurrence, and the manner in which this varies under altered conditions of life.

PROTOZOA

Among the Protozoa the organisms pass through successive phases of vitality, which are comparable to the different age-periods of the Metazoa. In such simple forms of life, fission or division into two parts is the usual method of reproduction,[3] and the frequency of its occurrence appears to depend more upon the phase which has been reached in the life-cycle, than upon the influences of the environment. Thus, there is a period of extreme vigour of cell-multiplication, corresponding to the youth of a metazoön; secondly, there is a period of maturity, characterised by changes in the chemical and physical properties of the cell, and leading to the formation of conjugating individuals; and finally, in forms which do not conjugate, there is a period of senescence which ends in death. It is interesting to note, however, that the rapidity of fission is affected by the temperature and the food; for example, an individual of the Ciliate Infusorian, *Stylonychia pustulata*, if well supplied with food, divides once in twenty-four hours in a temperature of from 5° to 10° C., and once in twelve hours in a temperature of from 10° to 15° C.[1] In *Paramœcium aurelia*, too, it has been found that the rate of reproduction is influenced by temperature after the manner of a chemical reaction.[2] Again, Flagellate Infusoria of different kinds have been induced to conjugate by changing the temperature or increasing the density in the surrounding medium.[3] Furthermore, the life-cycle of *Paramœcium* may be renewed without the occurrence of conjugation, that is to say, fission can be made to continue and senescence can be avoided, by introducing a change in the composition of the medium surrounding the culture.[4] (See p. 222.)

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[1] Darwin, *Variation of Animals and Plants*, Popular Edition, vol. ii., London, 1905.

[2] See especially page 18, where Bles's observations on the breeding habits of Amphibia are referred to.

[3] In this process no material is lost, and two simple nucleated organisms result. During the period of maturity referred to in the text, multiplication is often preceded by union (either temporary or complete) of two individuals, and this process is called conjugation (see p. 220, Chapter VI.).

Moreover, there is evidence that in the case of *Colpoda steini* at least the occurrence of conjugation is determined entirely by the conditions of the surrounding medium.

CŒLENTERATA

With the majority of the Metazoa, as already indicated, there is a more or less definitely restricted season to which the occurrence of the chief reproductive processes is confined.

Thus in the common hydra of Bengal (*Hydra orientalis*, Annandale), which, like most other Cœlenterates, reproduces by budding as well as by the sexual method,[5] the former process occurs chiefly during winter, the buds developing into new individuals. Towards the beginning of the hot weather budding becomes less active, and in some individuals ceases altogether, while the same thing happens during periods of temporary warmth in winter. A rise in temperature induces a proportion of the individuals present in an aquarium or pond to develop testes or male reproductive glands; if the rise is considerable it may cause a few of the remaining individuals to produce ova. On the other hand, no individual living in its natural environment has been known to exhibit any sign of sex after the rise in temperature had become steady. The conditions most favourable to the production of ova appear to be a period of comparatively low temperature and abundant nutrition followed by a sudden but not excessive rise of temperature.[1]

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[1] Sedgwick, *Student's Text-Book of Zoology*, vol. i., London, 1898.

[2] Woodruff and Britsell, "The Temperature Coefficient of the Rate of Reproduction of *Paramœcium aurelia*," *Amer. Jour. of Physiol.*, vol. xxix., 1911.

[3] Calkins points out that the same experiment is performed by mosquitoes and other insects on certain parasitic Protozoa, as when a parasite is withdrawn from the hot environment of the Mammalian blood into the comparatively cold region of the mosquito's alimentary tract. ("The Protozoan Life-Cycle," *Biol. Bull.*, vol. xi., 1906.)

[4] Calkins, *loc. cit.*

[5] Asexual reproduction is of very common occurrence among the majority of the lower animals and plants. It may take the form of simple binary fission (in unicellular organisms), of spore formation, or of germination or budding. Sexual reproduction consists essentially of the union of two cells

Some of the marine hydroids show an alternation of generations which does not appear at first sight to be in any way related to change in the environment. In such cases the fertilised ovum develops into a polyp which gives rise to a colony of polyps by a process of sexual reproduction. After the colony has reached a certain size, a new kind of bud is formed, and this becomes a jelly-fish. The latter, after leading an independent existence, produces eggs, and these in turn become fertilised, giving rise to a new generation of polyps. Morgan points out that as the polyp colony goes on increasing in size, its relation to its surroundings must undergo change, and that, very possibly, it is this change which determines the development of jelly-fish in place of polyps. If this interpretation is correct the breeding season among marine hydroids is controlled by environmental conditions, just as it is among most other animals.[2]

and their subsequent division to give rise to the new individual. In the multicellular organisms (Metazoa and Metaphyta) there are two kinds of conjugating cells, or gametes, which are specialised for the purpose. These are produced by the male and female respectively, and are known as spermatozoa and ova. Thus, sexual reproduction in the Metazoa is a modification of conjugation in the Protozoa. (See Chapter VI.)

[1] Annandale, "The Common Hydra of Bengal," *Memoirs of the Asiatic Society of Bengal*, vol. i., 1906. *Cf.* Whitney, "The Influence of External Factors in causing the Development of the Sexual Organs in *Hydra viridis*," *Arch. f. Entwick.-Mechanik*, vol. xxiv., 1907. Whitney says that in *Hydra viridis* an abundance of food following a low temperature causes a suppression of the formation of testes and ova.

[2] Morgan, *Experimental Zoology*, New York, 1907. Morgan shows that the same point is illustrated by certain recent experiments of Klebs on flowering plants. These at first produce only leaves and branches. When they reach a certain size they produce flowers. Klebs regards the development of the flowers as being due to a relation that becomes established between the plant (when it has reached a certain stage of growth) and the environment. He shows also that by altering the environment a shoot may be induced to go on growing vegetatively, when it would ordinarily develop into a flowering branch. The flowering of the plant, therefore, is not merely the culmination of its form, as most botanists regard it. For much valuable

Some interesting observations have been recorded by Ashworth and Annandale[1] about the breeding habits of sea-anemones. The species *Sagartia troglodytes* and *Actinia mesembryanthemum*, which are very prolific in captivity, have been noticed to breed regularly in the early spring. *Actinia* commences to produce young in the beginning of February, and *Sagartia* about a month later. As a rule the young are extruded in the early morning, and one individual may repeat the process every morning for a number of weeks, when the breeding season comes to an end. In one season, when the aquaria were somewhat neglected, the specimens of *Sagartia* produced fewer young than usual, and these were not extruded until the beginning of April. Specimens of *Actinia* living in the same aquaria were more prolific, but their breeding season was also somewhat retarded. In the month of August two anemones of the species *Sagartia troglodytes* were brought from Thorshavn in the Færoës, and placed in the aquaria. In the following October both of these produced several young; while in April of the next year one of them again gave birth, but only to a single anemone. It seems probable that in this case the change of temperature or environment had induced the anemones to breed at an unusual season; for it is unlikely that October is the normal period for reproduction in the Færoës, as by this time the sea has already begun to run high, and there would be a great risk of the young anemones becoming destroyed, being unable to attach themselves.

Ashworth has pointed out[2] that in the coral *Xenia hicksoni*, which lives in the tropics, there is every evidence that spermatozoa are discharged over a very considerable period, if not practically throughout the whole year, whereas in the related form *Alcyonium digitatum*, of Northern Europe, the period during which the spermatozoa are discharged is limited to about a month in the winter. Ashworth remarks that the difference is probably due to the fact that *Xenia*, living on reefs in the shallow waters of tropical seas, is not subject to great variations in temperature and food-supply, while with *Alcyonium* such variations are no doubt considerable. In a similar way Miss Pratt,[3] who has studied the process of oögenesis in *Sarcophytum*, *Holophytum*, and *Sclerophytum*, concludes that the sexually mature condition in these tropical genera extends over a

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and suggestive information on the factors which control breeding in plants G. Klebs' work should be consulted. (*Willkürliche Entwickelungsänderungen bei Pflanzen*, 1903.)

[1] Ashworth and Annandale, "Observations on some Aged Specimens of *Sagartia troglodytes*, and on the Duration of Life in Cœlenterates," *Proc. Roy. Soc. Edin.*, vol. xxv., 1904.

[2] Ashworth, "Structure of *Xenia hicksoni*," *Quar. Jour. Micr. Science*, vol. xlii.

[3] Pratt, "On Some Alcyonidæ," *Herdman's Ceylon Reports*, vol. iii.

considerably longer period than in the case of corals inhabiting temperate waters.

It may also be noted that, whereas in the Ctenophora of the Mediterranean the breeding season extends throughout the year, in members of the same class in northern seas it only lasts through the summer.[1]

NEMERTEA, ETC.

The breeding season and its relation to the environment have formed the subject of a careful investigation by Child[2] in the case of a small Nemertean, *Stychostemma asensoriatum*, which is found very abundantly in one of the park lagoons of Chicago. The season extends from May to November or December, according to the temperature of the water. Egg-laying can occur freely in the laboratory, the eggs being deposited always during the night, or in darkness, when the animals move about freely. Although breeding in the natural state is restricted to the warmer part of the year, eggs can be obtained in the laboratory at practically any time, by simply regulating the temperature. Thus egg-laying can be induced in the winter at ordinary room-temperature, even though the worms are kept without food. "In animals which contained only a few small oöcytes when taken, and which are kept in clean water without food, the growth of the oöcytes will continue, and within a week or two eggs may be laid." "The body of the animal may even decrease somewhat in size during the growth of the oöcytes." It is clear, therefore, that in *Stychostemma* the limits of the breeding season are determined chiefly by the temperature of the water, and that food is a factor of secondary importance.

Similarly, in the case of the parasitic Trematode, *Diplozoön paradoxum*, which ordinarily produces eggs only in the summer, it has been found that the formation of eggs could be artificially prolonged throughout the winter, if the fishes on whose gills the animal lives are kept in an aquarium at summer heat.[3]

ANNELIDA

Certain species of Polychæt Annelids, known as the Palolo worms, exhibit a quite remarkable regularity in the periodicity of their breeding habits. During their immaturity all the Palolos live in burrows at the bottom of the water. With the attainment of sexual maturity, and under certain peculiar conditions, they swarm out for purposes of breeding. In the Atlantic Palolo (*Eunice fucata*) and the South Pacific Palolo (*Eunice viridis*) the process invariably takes place twice, upon or near the day of the last quarter of the moon and with the first rays of the sun; but with the former species it occurs in June and July, and with the latter in October and November. The general conditions of existence for these worms would appear to be remarkably uniform, the temperature variation being from 24° to 30° only. In the Japanese Palolo (*Ceratocephale osawai*) the swarming takes place on nights closely following the new and full moons (*i.e.* when the spring tides occur), in October and November, the worms swimming out regularly four times a year. Each swarming-period lasts from one to four days. It has been noted further that the swarm is greater after the new moon (when the spring tide is highest) than after the full moon (when the tide is not so high), that each swarming takes place invariably just after the flood in the evening, that it continues for from one to two hours, and is generally larger on warm, cloudy nights than on clear, chilly nights. It would appear also that no individual worm takes part in more than one swarming in the year.[1]

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[1] Bourne, "The Ctenophora," *Treatise on Zoology*, vol. ii., London, 1900.

[2] Child, "The Habits and Natural History of Stychostemma," *American Naturalist*, vol. xxxv., 1901.

[3] Semper, *Animal Life*, London, 1881.

ARTHROPODA

Innumerable instances of the periodicity of breeding and its relation to seasonal and environmental changes might be adduced from the great group of Arthropods, but the reason for the variations which occur is not always obvious. Thus, in the common crayfish (*Astacus fluviatilis*), in France the males are said to approach the females in November, December, and January, whereas in England they begin to breed as early as the commencement of October, if not earlier.[2] Also, in the Cape species of *Peripatus* (*P. capensis*) birth takes place in a fixed season (during April and May), whereas, in the South American species, births are said to occur probably throughout the entire year.[3]

In the case of the hemipterous insect known as the plant-louse (*Aphis*), we have evidence that the mode of reproduction is dependent upon temperature. In a favourable summer the females of this animal may produce as many as fourteen consecutive generations of young by parthenogenesis, the ova undergoing development without being fertilised by the male. At the beginning of the winter male plant-lice make their appearance and fertilise the eggs, which develop in the succeeding spring. Réaumur, however, by artificially maintaining a constant summer temperature, succeeded in producing more than fifty parthenogenetic generations of plant-lice, all descended from a single mother.[1]

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[1] Izuka, "Observations on the Japanese Palolo," *Jour. of the College of Science, University of Tokyo*, vol. xvii., 1903. This worm is a Phyllodocid and not a true Palolo. Other swarming Polychætes are *Nereis dumerilii*, which swarms occasionally; *Nereis limbata*, in which each sex secretes a substance which activates the other, the males swarming first and being followed by the females; and *Odontosyllis enopla* (a Bermudan syllid), in which the female is phosphorescent intermittently at the hind end of the body, her appearance being followed by the male, the phosphorescence of the female ceasing after spawning is over. I am indebted to Mr. C. F. A. Pantin, of Christ's College, for this information.

[2] Huxley, *The Crayfish*, London, 1880.

[3] Sedgwick, "Peripatus," *Camb. Nat. Hist.*, vol. xii., London, 1901.

Morgan, however, describes some observations which seem to indicate that the change is not merely due to temperature. He shows, for example, that the sexual forms of Aphis may appear in the autumn before the onset of the cold weather, and conversely that many individuals may continue to reproduce parthenogenetically, until finally they perish from the cold. Morgan suggests that the alternation in the mode of reproduction may depend upon changes which take place in the food-plant in the autumn, instead of being solely a temperature effect. He shows also that there is evidence for the conclusion that in the genus *Chermes*, in which the alternation of generations occurs between the fir-tree and the larch, the conditions existing on the larch are those that call forth the sexual forms.[2]

It has been supposed that the change in the environment is also responsible for determining the sexes in aphids. Miss Stevens, however, has recently shown that what appears to be a change in sex should rather be regarded as a change from the parthenogenetic to the sexual mode of reproduction.[3] According to this view the sex of each individual is determined by the character of the gamete or gametes by which it is developed. The supposed influence of food and external conditions upon sex-determination in various kinds of insects, and other animals, is discussed at some length in a future chapter of this work (Chapter XV.).

Semper pointed out long ago that the occurrence of reproduction (or of the particular mode of reproduction), with insects as with other animals, depends, among other things, upon the nature of the diet, upon the chemical conditions of the surrounding medium, upon the moisture of the air, or upon other circumstances which are often unknown. Thus, failure to breed in a new environment is experienced by many Lepidoptera. For example, Death's-Head hawk moths, which are commonly blown over to this country from the Continent, but do not breed here continuously, deposit their eggs on young potato plants, and these develop into moths which emerge in the autumn. These moths; however, are quite infertile, so that, as a result, the Death's-Head has never established a permanent footing in Britain, though stray specimens are often captured.[1] In the case of other insects, such as the mosquito (*Anopheles*), there is direct evidence that food is an important factor in egg-formation. Thus it was found that mosquitoes fed on bananas refused to breed, but when fed on human blood they invariably laid eggs after two or three days.[2] It is interesting to note also that in the mosquitoes and other Culicidæ, the males are generally unable to suck blood, this habit being apparently correlated with the function of oviposition. Among the Empidæ, which are carnivorous, the females, during the nuptial flights, are always fed by the males on small insects, and they seem incapable of discharging their sexual functions unless they are fed in this way.[3] The Hon. Charles Rothschild, however, has suggested a more probable explanation of this phenomenon, namely, that the females would eat the males were they not supplied by a specific pabulum to divert their attention.[4] Howlett[5] has shown that with the fruit-fly of Pusa (*Dacus*) sexual attraction is brought about by an odour emitted by the female and that this can be imitated artificially by oil of citronella.

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[1] Semper, *loc. cit.*

[2] Morgan, *loc. cit.*

[3] Stevens, "Studies in the Germ-Cells of Aphids," *Carnegie Institution Report*, Washington, 1906.

In some insects oviposition takes place long after the death of the males. Thus, Lefroy and Howlett state that in the mango weevil (*Cryptorhynchus gravis*) the males die in August while the females live until the following March to lay eggs.[6]

MOLLUSCA

Among the marine Mollusca, in curious contrast to so many forms of life, winter is the usual time for the deposition of the eggs.[7] On our own coasts Nudibranchs come to shore to lay their eggs from January to April. *Patella* spawns from October until the end of the year. *Purpura lapillus* is said to be most active during the same season, but it breeds to some extent throughout the year. *Buccinum undatum* breeds from October until May, whereas *Littorina* breeds all the year round.[8]

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[1] *Country Side*, October 27, 1906.

[2] "Report of Malaria Expedition to Nigeria," Liverpool, *Trop. Med. Memoir*, IV. See also Ross (*Nature*, vol. lxxx., 1909), who says that females of *Culex* and *Stegomyia* apparently only desire to suck blood after fertilisation.

[3] Howlett, "Coupling of *Empis*," *Ent. Mag.*, vol. xliii., 1907.

[4] Letter to the author.

[5] Howlett, "The Effect of Oil of Citronella on two species of Dacus," *Trans. Ent. Soc. Lond.*, 1912.

[6] Lefroy and Howlett, *Indian Insect Life*, Calcutta, 1909.

[7] Lo Bianco, "Notizie biologische riguardanti specialmente il periodo di maturità sessuale degli animali del golfo di Napoli," *Mitth. Zool. Stat. Neapol.*, vols. viii. and xiii. Much valuable information concerning the breeding habits of Mollusca and other animals, inhabiting the Bay, is given in these papers. See also vols. xviii., xix., and xx.; and Isset, *Biologia Marina*, Milan, 1918.

[8] Cook, "Mollusca," *Camb. Nat. Hist.*, vol. iii., London, 1895.

Among the land-Mollusca there is a more marked periodicity in the breeding season than among the marine forms. In temperate climates breeding is restricted to the summer. In the tropics the occurrence of the breeding season is generally determined by the alternations of wet and dry seasons. In other cases, where there are no great seasonal changes, the land-Mollusca may breed all the year round.[1] The snails of the Mediterranean area, according to Semper, arrive at sexual maturity when they are six months old, and before they are fully grown. Those individuals which reach this age in the spring deposit eggs a second time after the heat of the summer is over, and so experience two breeding seasons in the year, with an interval of a few months between them during the hot weather. Semper shows, further, that individuals of the same genera, or perhaps even of the very same species, in the damper and colder climates of the north, do not lay eggs till development is complete; while in the dry, warm region of the Mediterranean, they have produced two lots of eggs before they are fully grown. This is because completion of growth and sexual maturity do not necessarily coincide. In a similar way, in the pond-snail (*Limnæa*) the minimum of temperature which admits of the assimilation of food, and so of growth, is much above the winter temperature of egg-deposition.

In tropical climates, where the variation in temperature throughout the year is reduced to a minimum, the periodicity in the breeding habits of animals is to a considerable extent obliterated, at least in so far as it is dependent upon temperature. Semper[2] says that few things impressed him more in the Philippine Islands than the absence of all true periodicity in the breeding habits not only of the land-molluscs, but also of the insects and other land-animals. "I could at all times find eggs, larvæ, and propagating individuals, in winter as well as in summer. It is true that drought occasions a certain periodicity, which is chiefly perceptible by the reduced number of individuals in the dry months, and the greater number in the wet ones; it would seem that a much smaller number of eggs are hatched under great drought than when the air is very moist. Even in January, the coldest and driest month, I found land-snails which require much moisture, and at every stage of their development, but only in shady spots, in woods, or by the banks of streams. But what was far more striking in these islands was the total absence of all periodicity in the life of the sea-animals, particularly the invertebrata; and among these I could not detect a single species of which I could not at all seasons find fully grown specimens, young ones, and freshly deposited eggs." Semper goes on to remark that

[1] Semper, *loc. cit.*

[2] Semper, *loc. cit.*

even in some cold seas periodicity is far more often eliminated than is commonly supposed, and mentions that the eggs of the sea-mollusc, *Tergipes*, have been found at all seasons, like those of *Littorina* on our own coasts. (*Cf.* p. 29.)

ECHINODERMATA

Sea-urchins and starfish, and other *Echinodermata*, appear generally to have a regularly recurrent breeding season, at which the genital organs swell up to an enormous size. In the sea-urchin, *Echinus esculentus*, these organs grow into huge tree-like structures with branched tubes, lined by the sexual cells. These are sold for food by the fishermen in Naples, who call them "frutta di mare." It is said that a single female *E. esculentus* will produce as many as 20,000,000 eggs in a breeding season. At other times of the year the generative organs are so reduced as to be scarcely recognisable. *E. esculentus* at Port Erin, in the Isle of Man, spawns in June.[1] At Dunbar, in Scotland, it has been observed to spawn at the same time. The sea-urchins at Naples spawn at the end of the year (*E. acutus* being mature in November and December, and *E. microtuberculatus* from September onwards).[2] Fox has written as follows concerning the Mediterranean and Red Sea species:—

"The sea-urchins at Suez (*Diadema serosum*) breed from the spring until September. During this season the genital products are developed in cycles correlated with the lunar periods. Spermatozoa and eggs are discharged into the sea between the first and third quarters of each moon, the majority of individuals spawning about the time of full moon. The greater number of specimens examined between the first quarter and full moon have the gonads swollen and filled with spermatozoa or eggs in a state ready for discharge into the sea, while a smaller number show that the genital products have lately been shed. As the third quarter of the moon approaches, whereas some individuals still have testes or ovaries full of spermatozoa or eggs, most have already spawned. After the third quarter all have extruded their genital products, and the gonads, now smaller in size, contain numerous spermatocytes or oöcytes in the process of development into spermatozoa or eggs, to be shed into the sea round about the next full moon. From the new moon until the first quarter following it the gonads are filled with spermatocytes or oöcytes in a more advanced stage of development, and, in addition, there are present in some individuals spermatozoa and unripe or ripe eggs. After this the same cycle is repeated.

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[1] Chadwick, *Liverpool Marine Biological Committee Memoirs*, vol. iii., *Echinus*, Liverpool, 1900.

[2] Lo Bianco, *loc. cit.* The spawning times of most of the Naples Echinoderms are given in these memoirs.

"The gonads of sea-urchins are eaten in different parts of the world, and the variation in their size, corresponding with the phases of the moon, is common knowledge in the fish markets of the Mediterranean and elsewhere. The same fact is referred to by Aristotle[1] and other classical writers, both Greek and Roman."[2]

CEPHALOCHORDATA

In the lancelet (*Amphioxus lanceolatus*) of the Mediterranean the breeding season extends from spring until autumn, the glands becoming so large by the ripening of ova and spermatozoa that the atrium is used up to its utmost capacity. Spawning, when it occurs, invariably takes place about sun-down (*i.e.* between 5 and 7 P.M.), and never, so far as known, at any other times.[3]

PISCES

Among fishes the duration of the breeding season varies considerably according to the group to which they belong. The ova of *Elasmobranchs* are deposited singly or in pairs at varying intervals throughout a great part of the year. In *Teleosts*, on the other hand, the breeding season is limited as a rule to the spring and summer in temperate climates. In a single individual spawning may last no longer than a few weeks or even days.[4] The enormous number of eggs produced by most *Teleosts* must be connected with the absence of internal fertilisation, involving a large wastage of ova which never come in contact with male cells or spermatozoa.

The cod, off our own coasts, has a spawning season extending from January to June, but the majority of individuals spawn in March. It has been found, however, that in some parts of the North Sea the cod may spawn in the autumn. In the whiting the spawning period lasts from early March until the third week in August.[5] The investigations of the Marine Biological Association have shown that in the plaice of the South Devon bays the maximum spawning period is between the third week of January and the second week of February. This period in the North Sea and Irish Sea would appear to be slightly later. Herdman[6] records that, in the year 1904, the plaice in the open-air ponds at the Port Erin Biological Station started spawning on 3rd March, and those at the Peel (Lancashire) Sea Fish Hatchery (under cover) on 1st March.

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[1] *The Works of Aristotle*, vol. iv., *Historia Animalium*, D'Arcy Thompson's Translation. Oxford, 1910. And see footnote by the translator.

[2] MS. by Mr H. Munro Fox, Fellow of Gonville and Caius College, to whom the author is indebted for this information.

[3] Willey, *Amphioxus and the Ancestry of the Vertebrates*, New York, 1894.

[4] Bridge, "Fishes," *Camb. Nat. Hist.*, vol. vii., London, 1905.

[5] Masterman, "A Contribution to the Life-Histories of the Cod and Whiting," *Trans. Roy. Soc. Edin.*, vol. xl., 1900.

[6] Herdman, "Spawning of the Plaice," *Nature*, vol. lxix., 1904. See also Wallace (W.), same volume. For information concerning the spawning seasons of different species of fish, *The Journal of the Marine Biological Association*, the

In the Holostean fish, *Lepidosteus*, which lives in the fresh waters of North America, the breeding season recurs with a wonderful regularity about May. At this time the fish resort in large numbers to shallower water, where the temperature is higher. Here the ova and spermatozoa are emitted during recurrent periods of sexual excitement.[1] The related fish *Amia*, of Central and Southern North America, spawns usually in May, the exact season depending somewhat upon the temperature of the water. The fish make their way from deep water to the shallow spawning place, which is generally at the end of a swampy lake.[2]

In the Crossopterygian fish, *Polypterus bichir*, the ova ripen in the summer months from June to September, the breeding season depending upon the period of inundation, as in most of the Nile fishes.[3] The other species of *Polypterus* (*P. senegalis* and *P. lapradii*), which inhabit the river-basins of tropical Africa, spawn also in the wet season in July and August.[4]

In the Dipnoan, *Ceratodus*, of Australia the principal time for spawning is September and October, at the end of the dry season.[5] In the other two Dipnoans, *Lepidosiren* of South America and *Protopterus* of Africa, spawning occurs shortly after the emergence of the fish from their summer sleep. Kerr, writing of the former, says that the exact time for breeding varies greatly from year to year in correlation with the extreme variability of the climate, the swamps, which the mud-fish inhabit, sometimes remaining dry for prolonged periods.[6]

Many fishes migrate, before the commencement of the breeding season, to localities suitable for the deposition of their eggs. Thus, certain marine fishes like the salmon, the shad, and the sturgeon ascend rivers for long distances before spawning; others merely migrate to shallower water nearer shore. The eel, on the other

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publications of the English and Scottish Fishery Boards, and the International Council for Fishery Investigation, should be consulted. These reports show that the migratory and reproductive periods of fishes are affected by the temperature, salinity, etc., of the sea.

[1] Agassiz, "The Development of Lepidosteus," *Proc. Amer. Acad. Arts and Science*, vol. xiv., 1878.

[2] Bashford Dean, "The Early Development of Amia," *Quar. Jour. Micr. Science*, vol. xxxviii., 1895.

[3] Harrington, "The Life-Habits of Polypterus," *American Naturalist*, vol. xxxiii., 1899.

[4] Budgett, "On the Breeding Habits of some West African Fishes," *Trans. Zool. Soc.*, vol. xvi., 1901.

[5] Semon, *In the Australian Bush*, London, 1899.

[6] Kerr, "The External Features in the Development of *Lepidosiren paradoxa*," *Phil. Trans.*, B., vol. cxcii., 1900.

hand, is a fresh-water fish which migrates to the sea for breeding, and deposits its eggs in deep water (in spring and early summer).[1]

Jacobi[2] showed that the migration of the eel is not determined by the growth of the genital organs, for these do not begin to develop until the fish have reached the sea. He concluded, therefore, that eels need salt water before the genital organs can develop. Similarly, Noel Paton[3] has pointed out that salmon, with their genitalia in all stages of development, are ascending the rivers throughout the whole year.

Miescher,[4] too, has shown that salmon go practically without food so long as they are in fresh water, being nourished by the large store of material which they accumulated while they were in the sea. This observation has been confirmed by Noel Paton. Miescher and Paton have shown, further, that the gain in solid material (proteins, etc.) by the genitalia,[5] as the fish pass up the rivers, is met by a loss in solid material in the muscles. This transference is not brought about by anything of the nature of a degeneration taking place in the muscles; but the latter appear simply to excrete or give out the material which has been accumulated in them. It should be noted, however, "that the gain of solids by the genitalia is small as compared with the loss of solids by the muscle, that in fact the greater part of the solids lost from the muscles are used up for some other purpose than the building up of the genitalia."[6] Paton concludes that the state of nutrition is the main factor determining migration towards the river, and that, when the salmon has accumulated a sufficiently large store of material, it returns to the rivers which were its original habitat. It does not seem possible, however, to maintain that nutrition is a determining influence in the growth of the genital glands, since these are undeveloped when the fish begin to migrate and enter upon their period of starvation.

Wiltshire[7] states that in some fishes, at the period of ovi-position, the lips of the genital orifice swell and become congested. This condition he regards as comparable to that which occurs during the "heat" period of a mammal.

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[1] Schmidt (J.), "The Breeding Habits of the Eel," *Phil. Trans.*, B., vol. ccxi., 1922.

[2] Jacobi, *Die Aalfrage*, Berlin, 1880.

[3] Paton, *Fishery Board Report of Investigations on the Life History of the Salmon*, Glasgow, 1898.

[4] Miescher, *Histochemische und Physiologische Arbeiten*, vol. ii., Leipzig, 1897.

[5] The gain in the genitalia is due largely to the formation of comparatively simple proteins (protamines, histones, etc.). See Chapter VIII.

[6] Paton, *loc. cit.* Milroy ("Chemical Changes in the Muscles of the Herring during Reproductive Activity," Seventh International Congress of Physiologists, Heidelberg, 1907; abstract in *Zent. f. Phys.*, vol. xxi., 1907; and *Biochem. Jour.*, vol. iii., 1908) has recently shown that similar changes take place in the herring, in which, however, the starvation period is briefer.

[7] Wiltshire, "The Comparative Physiology of Menstruation," *Brit. Med. Jour.*, 1883.

AMPHIBIA

The intimate connection between sexual periodicity and climatic variation exhibited by many Amphibia and Reptilia, especially in temperate climates, was commented on by Spallanzani.[1] This close dependence upon environmental conditions is evidently due largely to the habits of life of these animals, many of which hibernate or show great sluggishness in cold weather; while among Amphibia it must be associated with the further fact that, whereas most members of the group live to a great extent upon land, it is necessary for them to deposit their eggs in water. Spallanzani concludes that the reason why Amphibia are subject to a variation which is not observable in birds and Mammals is because the former, like insects, are cold-blooded, and have a comparatively small supply of internal heat to animate them when it is cold. "As therefore the exercise of their functions depends on the heat of the atmosphere, their amours will also depend upon this cause, and will, of course, be later in cold than in hot climates, and in both will vary with the season."

Spallanzani illustrates the truth of this fact by pointing out that various species of frogs and toads begin to propagate earlier in Italy than in Germany or Switzerland.[2] On the other hand he records the observation that the tree-frog and the fetid terrestrial toad were copulating in the ponds and reservoirs of Geneva in March, at a time when in Lombardy they had not yet quitted their subterranean abodes.

It is interesting to note that in the frog and other Amphibia the ova are produced in winter, when the animals eat little or nothing, just as the genital organs of the salmon develop during the period of migration, when the fish have practically ceased to feed.

Bles[3] has discussed at some length the conditions under which it is possible to induce various species of Amphibia to breed in captivity. He states that the most necessary condition is that the animals should be allowed to hibernate at the proper season, and in order to accomplish this they must be in thoroughly good health when the winter sets in, having passed the summer in the best circumstances in regard to light, heat, and supply of food. Bles's observations relate more especially to the African frog, *Xenopus lævis*, but he believes his conclusions to apply in a large degree to many other species of Amphibia.

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[1] Spallanzani, *Dissertations*, vol. ii., London, 1784.

[2] In the common frog (*Rana temporaria*) the usual time for spawning in Middle Europe is March, earlier in warm, later in cold seasons; in southern countries, January or February, but in Norway not until May. *Vide* Gadow, *Camb. Nat. Hist.*, vol. viii., London, 1901. This book contains a quantity of valuable information concerning the breeding habits of many Amphibia and reptiles.

[3] Bles, "The Life-History of *Xenopus lævis*," *Trans. Roy. Soc. Edin.*, vol. xli., 1905.

The frogs in question were kept in a "tropical aquarium" (that is to say, an aquarium which could be kept at a tropical temperature by regulating a heating apparatus). In the summer the temperature was maintained at about 25° C.; in December it was allowed to drop to 15°-16° C. during the day, and 5°-8° C. during the night. The bottom of the aquarium was covered with earth and stones, on which the weed *Vallisneria* thrived. The water in the aquarium was never changed. The frogs were fed daily upon small worms, or strips of liver, until they would eat no more. During winter they became lethargic, taking very little food. When the temperature rose in the spring and the days became brighter, the frogs became more active, especially the males. At this time breeding could be induced by a certain method of procedure which Bles describes as follows: "First, the temperature of the aquarium is raised to 22° C.; and secondly, when it has become constant, a certain amount of water, say two gallons, is drawn off morning and evening, allowed to cool for twelve hours, and then run in slowly in the following manner, in order to simulate the fall of rain. The cooling vessel is raised above the level of the aquarium, and a syphon is used to run off the water. The lower end of the syphon is drawn out to a fine point, and turned up in such a way that the water rises up like from a fountain, and falls as spray into the aquarium. . . . By carrying out such measures I obtained from one female, between April and July 1903, more than fifteen thousand eggs."

The abdomen of the female *Xenopus* is stated to become very much distended during the winter by the enormously enlarged ovaries. "The three flaps surrounding the cloacal aperture are flaccid until the spring, when they become swollen and turgid, and more highly vascularised." (*Cf.* the changes in the female genital organs of Mammals during the "heat" periods, described in the next chapters.) The male *Xenopus* is said to assume its nuptial characters two days after the temperature is raised to 22° C., and a very little later it becomes vocal, the voice strengthening from day to day. Copulation takes place only at night, and spawning may commence an hour afterwards; but this does not occur unless the water is changed in the manner above described.

According to Leslie[1] it would appear that *Xenopus*, in its native country, breeds only in August, *i.e.* in the South African spring. Bles, however, is disposed to think that *Xenopus*, like *Discoglossus* in the wild state, may breed several times during the spring and summer, since the frogs in confinement in some years spawned three times.

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[1] Leslie, "Notes on the Habits and Oviposition of *Xenopus lævis*," *Proc. Zool. Soc.*, 1890.

Semper[1] has shown that if axolotls are kept crowded together in small aquaria, without plants or seed, individuals which are sexually mature will not deposit ova even though the water be changed and abundant food supplied. But if they be suddenly transferred to aquaria stocked with plants, and with stones and sand on the bottom and running water, they can be induced to spawn within a few days, and may do so as often as three or four times a year. Bles states that he is able to confirm Semper's observations upon axolotls, and that he obtained similar results by treating individuals of *Triton waltlii* and of *Discoglossus* in the same way.

Annandale[2] states that in the Malay Peninsula *Rhacophorus leucomystax* and *Rana limnocharis* appear to breed only after a heavy fall of rain, and he concludes that the stimulus set up by falling water is necessary before the sexual impulse can be induced.

Thus there appears to be abundant evidence that breeding in mature Amphibians does not occur cyclically merely, but it takes place only in response to certain definite external stimuli. Bles remarks that if this view is correct, and assuming it to apply to other groups besides the Amphibia, it helps to explain why many animals fail to breed in captivity; and also how it is that others (*e.g.* insects), in a state of nature, appear in large numbers in one year and are much less numerous in another.[3]

It is interesting to note that among frogs and other cold-blooded Vertebrates there is a periodicity in the occurrence of their reflex responses.[4] It has been shown that if the region of the shoulder-girdle bearing the four limbs, together with the connected skin and muscles, and the three upper segments of the spinal cord, are cut out from the male frog during the breeding season (but not at other times), the irritation of the skin will cause a reflex, clasping movement, similar to that characteristic of the normal male at this period. In spring and early summer, after reviving from their winter sleep, frogs tend to be irregular in certain other of their reflex responses. MacLean has shown that in the heart of the frog, newt, and salamander, and also the eel, vagus inhibition is absent or markedly diminished at certain periods corresponding roughly to the seasons of sexual activity,[1] but the significance of the changes is not very apparent.

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[1] Semper, "Ueber eine Methode Axolotl-Eier jederzeit zu erzeugen," *Zool. Anz.*, vol. i., 1878. See also *Animal Life.*

[2] Annandale, *Fasciculi malayenses*, *Zool.*, Part I., 1904.

[3] See p. 5, Chapter I.

[4] The sexual posture of frogs in the act of copulation is maintained as a spinal reflex. The tortoise is similar. The reflex is inhibited by excitation of the optical lobes. (Spallanzani, *loc. cit.*; Goltz, *Zeit. f. deutsch. med. Wiss.*, 1865-66; Tarchanoff, *Pflüger's Arch.*, vol. xl., 1887; Albertoni, *Arch. Ital. de Biol.*, vol. ix., 1887.)

REPTILIA

Reptiles which hibernate usually begin to breed shortly after the commencement of the warm weather which terminates the hibernating period, just as in the case of Amphibia. Other reptiles, which live in warm or tropical climates, also have regularly recurrent breeding seasons, in some cases extending over many months, generally in the spring and summer.[2] It would seem that in reptiles also breeding only occurs in response to certain external stimuli, and that temperature is the main factor, as supposed by Spallanzani.

AVES

It would appear almost superfluous to cite examples of sexual periodicity from among birds. That spring and summer are the seasons when most birds pair, build their nests, and incubate their eggs, and that these processes are wont to vary slightly with the character of the season, are facts that are familiar to all. Bird-fanciers know also that the capacity of certain birds for egg-laying may be influenced by diet, and that this capacity can sometimes be increased (*e.g.* in the common fowl[3]) by the supply of suitable food. However, in the domestic fowl the production of eggs is mainly influenced by the season of the year, the maximum production taking place in the months of March and April, and the minimum in October and November. In very high producing strains Pearl and Surface[4] found that there is an additional egg-laying season in the autumn months. The time of maximum production is influenced by climatic conditions. Thus Buckley[5] found in the South of England that this occurred in March and April, whereas in places where the spring is later the maximum is not attained so soon, and it is well known that the time of greatest production is earlier if the birds are given shelter.[1]

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[1] MacLean, "The Action of Muscarin and Pilocarpin on the Heart of certain Vertebrates, with Observations on Sexual Changes," *Biochem. Jour.*, vol. iii., 1908.

[2] See Gadow, *loc. cit.*

[3] Wright, *The New Book of Poultry*, London, 1902.

[4] Pearl and Surface, *U.S. Dep. Agric. Bureau, Animal Industry*, Bull. 110, 1911.

[5] Buckley, *Farm Records and the Production of Clean Milk at Moundsmere.*

With the approach of the breeding season the genital organs grow enormously until the whole oviduct reaches a state of hypertrophic turgescence. Gadow states that in the common fowl the oviduct at the period of rest is only six or seven inches long and scarcely a line wide, but that at the time of egg-laying it becomes more than two feet in length and nearly half an inch in width, thus increasing the volume about fifty times. This remarkable growth occurs annually. Gadow remarks also that the testes of the house-sparrow increase from the size of a mustard-seed to that of a small cherry, and in so doing temporarily displace the usual arrangement of the viscera in the body-cavity.[2]

A very large number of birds seasonally migrate, and this habit, as in the case of the migratory fish already referred to, is closely associated with the function of breeding.[3] Jenner[4] stated long ago that migration was invariably associated with an increase in size of the ovaries and testes, and that when these begin to shrink, after discharging their functions, the birds take their departure. Thus the ovaries of the cuckoo are stated to be almost atrophied in July. It would seem quite possible that the annual development of the sexual organs is the immediate stimulus which, in the individual, fixes the time for the spring migration, for it is known that in birds passing northward the ovaries and testes are well developed. (But *cf.* fishes, p. 17). Thus wading birds, such as the sanderling shot by Dr. Eagle Clarke at Spurn Head, in May, were found by him to have their sexual organs in a very advanced state of growth. These birds were probably on their way to Greenland or Siberia.

Schafer[5] has suggested that the migratory impulse is determined by the relation of daylight to darkness, having been brought into being through the agency of natural selection, in consequence of the necessity to most birds of daylight for the procuring of food. This hypothesis explains both the northerly migration in spring and the southerly migration in autumn, since at both times the birds are travelling in the direction of increased light (or, if they start before the equinox, towards regions where they will enjoy longer daylight later in the season). The suggestion that the time of the spring migration is determined in each individual by a stimulus set up by the growing genital organs is in no way opposed to Schafer's theory, which provides an explanation of the general fact of migration.

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[1] Simpson, "An Investigation into the Effects of Seasonal Changes upon Body Temperature," *Proc. Roy. Soc. Edin.*, vol. xxxii., 1912. That the periodicity is not simply due to temperature is shown by the *Cereopsis* goose of Australia which, when brought to this country, lays its eggs in the autumn and hatches them in the winter, or at the same time as the Australian summer. *Cf.* black swans, see p. 24.

[2] Gadow, Article on "Reproductive Organs," in Newton's *Dictionary of Birds*, London, 1893-96. Disselhorst also ("Gewichts- und Volumszunahmen der männlichen Keimdrüsen," *Anat. Anz.*, vol. xxxii., 1908) has called attention to the enormous increase in size and weight of the testicles and ovaries in many birds (and also in some Mammals) in the breeding season. Thus, in *Fringilla*, the testicles may increase three-hundredfold.

[3] For much of the information given here regarding migration, I am indebted to Dr. Eagle Clarke.

[4] Jenner, "Some Observations on the Migration of Birds," *Phil. Trans.*, Part I., 1824. See also John Hunter, *Animal Œconomy*, London, 1786.

[5] Schafer, "On the Incidence of Daylight as a Determining Factor in Bird Migration," *Nature*, November 7, 1907.

It has been noted that the northerly spring migration is far more hurried than the somewhat leisurely autumn migration in the reverse direction. Furthermore, although the north-south migratory movements are as a rule extraordinarily regular, it has been observed that the birds do not all set out together, and that the times of departure and arrival for each species may vary in any one year by several weeks. Moreover, golden plover are found migrating across Britain on their way northward (perhaps to Iceland) at a time when other individuals of the same species are rearing young in Britain. (The breeding season in Iceland is about a month or six weeks later than in Britain.) In view of these facts it is evident that the occurrence of the migratory movement is dependent not merely upon external or environmental influences, but also upon internal or individual ones, and, as already stated, it is not improbable that one of the factors involved is the state of development of the organs of generation.

Many birds are double-brooded, having young ones not only in spring, but also in autumn before the close of the mild weather (in temperate climates). Swifts are stated to have a second brood in Southern Europe after leaving Britain in August, and the same is said to be the case with nightingales. Wiltshire[1] mentions that a pair of swifts that stayed behind the others, had a brood in September, which migrated with the parent birds in October. Whether birds are single- or double-brooded probably depends to a large extent upon the duration of the period of incubation. This period in wading birds and sea-birds is approximately double that of passerine birds; but, within the limits of the group to which they belong, it is closely related to the size of the birds, the size of the egg, and the temperature of the bird.[2] Thus the incubation-period of the stormy petrel is thirty days; that of the starling is fifteen or sixteen days; while that of the raven (the largest passerine bird) is about nineteen days. The starling is, as a rule, almost certainly double-brooded, while the petrel and the raven are single-brooded.[1] Other birds, such as the sparrow, are probably often treble-brooded. It is, of course, well known that domestication tends to increase the number of broods which a bird may produce (*e.g.* in pigeons and poultry). In some cases, however, domestication has had the opposite effect, *e.g.* those breeds of poultry such as the non-sitting breeds which produce large numbers of eggs but have lost the power of brooding them. Broodiness in fowls is most frequent in spring and summer, the time of greatest egg-production, and is associated with warmth.[2]

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[1] Wiltshire, *loc. cit.*

[2] Bergtold, *A Study of the Incubation Period of Birds*, Denver, 1917.

Mammalia

The breeding season in the Mammalia, and the variations in its periodicity, are discussed at some length in the next chapter. Here it will suffice to point out that whereas the occurrence of breeding in any one country or locality is closely connected with the climatic conditions and the periodicity of the seasons in that country, this rule does not hold invariably. For while the sheep in South Africa breeds in April and May (the South African autumn), thus following the seasons (since sheep breed ordinarily in autumn in this country), the camels in the Zoological Gardens in London experience rut in early spring, or at approximately the same time as the breeding season of the wild camels in Mongolia.[3] It has been already noted that some Mammals refuse to breed in captivity, while in many others the occurrence of breeding can be regulated to some extent by such factors as accommodation, heating, and feeding. Also in certain domestic animals, such as the sheep, the condition of "heat" can be induced more readily by the supply of additional or special kinds of food.[4]

Associated Phenomena

The approach of the breeding season in many animals, if not in most, is marked by a display of greater vitality, as manifested by an increased activity, which relates not merely to the sexual organs but to the whole metabolism of the body. This enhanced vitality is, as a rule, maintained throughout the breeding season. Thus male birds at the time of pairing are in a state of the most perfect development, and possess an enormous store of superabundant energy. Under the influence of sexual excitement they perform strange antics or rapid flights which, as Wallace remarks, probably result as much from an internal impulse to exertion as from any desire to please their mates. Such, for example, are the rapid descent of the snipe, the soaring and singing of the lark, the strange love-antics of the albatross, and the dances of the cock-of-the-rock, and of many other birds.[1] The migratory impulse, which, as already mentioned, is closely associated with the periodic growth of the sexual organs, may also very possibly be regarded as affording evidence of increased vitality at the approach of the breeding season. Moreover, many of the secondary sexual characters, both those of the embellishing kind and others as well, are developed during only a part of the year, which is generally the period of breeding.

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[1] I am indebted to Dr. Eagle Clarke for certain of this information.

[2] See Gordon, *Jour. Amer. Assoc. Inst.*, and *Invest. Poultry Husbandry*, No. 3, 1915.

[3] Heape, "The Sexual Season of Mammals," *Quar. Jour. Micr. Science*, vol. xliv., 1900. The black swans in the Zoological Gardens breed at the same time as those in Australia. (*Cf.* also Timor pony, p. 46, and goose, p. 22.)

[4] *Cf.* birds, p. 21, and insects, p. 12. This point is referred to more fully in Chapter XIV., where the causes which influence fertility are discussed.

A familiar example of this correspondence between the development of secondary sexual characters and the activity of the reproductive organs is supplied by the growth of the antlers in stags. At the time of rut, which in the red-deer (*Cervus elaphus*) begins in September or October (see p. 44), the antlers, or branched outgrowths from the frontal bones, are completely developed, having shed their "velvet" or covering of vascular skin. The animals during this season are in a state of constant sexual excitement, and fight one another with their antlers for the possession of the hinds.[2] By the end of the year the fighting and excitement have ceased, and the stags begin once more to herd together peaceably, and apart from the females. Shortly afterwards the antlers are shed. In most parts of Britain this occurs about April; but a Highland stag has been known to drop his antlers as soon after the rutting season as December, while, on the other hand, some immature animals in the Lake District are said to carry them until May. After the shedding of the antlers new ones begin to grow from the pedicles, the growth taking place chiefly in July and August. When the new antlers have reached their full development the "velvet" is shed (about the beginning of September). The size of the antlers, and the number of branches or "points," go on increasing every year throughout the reproductive period of the stag's life and until he begins to decline with old age.[3]

In the American prongbuck (*Antilocapra americana*), which is unique among hollow-horned ruminants in shedding the horns every year, the shedding follows the rutting season more closely than in the stag. The rutting in this species begins in September, and lasts about six weeks. In old bucks the horns are shed in October, while the new growth is not completed until July or August in the following year.[1]

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[1] Wallace (A. R.), *Darwinism*, London, 1890.

[2] The larynx also is said to enlarge at this season, when the stag is wont to utter a loud bellowing noise.

[3] Cunningham (J. T.), *Sexual Dimorphism*, London, 1900.

A secondary sexual character of a comparable kind occurs in the male salmon, in which the tip of the lower jaw, during the breeding season, is turned up and enlarged, as if to protect the fish in fighting when charged by another male.[2]

In *Polypterus*, during the breeding season, the anal fin of the male becomes greatly enlarged and thickened, and has its surface thrown into folds between the fin-rays. The object of this modification is not known.[3]

The papillæ on the hind limbs of the breeding male *Lepidosiren* are structures which seem to possess a special significance, since Kerr[4] has shown that they probably serve as accessory organs of respiration. During the greater part of the year they are relatively inconspicuous; but as soon as the animal is set free at the beginning of the wet season, they begin to grow with remarkable rapidity, forming slender filaments two or three inches in length and blood-red in colour from their intense vascularity. After the breeding season is over the filaments commence to atrophy, and eventually shrink to their former size, but still present for some time a distinctive appearance owing to their being crowded with black pigment-cells. Whatever may be the precise purpose of this curious modification it is certain that its development is associated with reproductive activity, and so may be regarded as an expression of the intense vitality which the organism exhibits at this period.

Some animals exhibit in the breeding season a particularly vivid coloration which is absent from them at other times. The case of the male dragonet (*Callionymus lyra*), which becomes a brilliant blue-and-yellow colour, has been discussed at some length by Cunningham,[5] who concludes that the production of the guanin and pigment that give rise to the colour is to be connected with the intense nervous excitement which affects the fish at the time of courtship. "Physiological processes are known to be governed largely by nervous impulses, and not merely the circulation, but the excretory activity of the skin, are known to be influenced by nervous action. Pigment and guanin are produced in the skin by the secretory or excretory activity of the living cells."[6] Whatever be the precise explanation of this particular instance of intenser coloration, there can be no doubt that it is an indication of a more active metabolism.

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[1] Cunningham (J. T.), *loc. cit.*

[2] Darwin, *Descent of Man*, Popular Edition, London, 1901.

[3] Budgett, *loc. cit.*

[4] Kerr, *loc. cit.*

[5] Cunningham (J. T.), *loc. cit.*

[6] Cunningham (J. T.), *loc. cit.*

The brilliant colours of the male lump-sucker (*Cyclopterus lumpus*), and of other fish[1] at the time of breeding, are probably due to the same causes as in the dragonet.[2]

The tail of the lyre-bird, which is shed at the end of the breeding season, not to be renewed again in the same form until the following summer, the brilliant plumage of the breeding drake, the more intense colouring of the phalarope, and many other birds during the season of courtship, are familiar instances of the same kind of phenomena.[3] The remarkable plate of horn which is developed in the upper mandible of the pelican in the breeding season, and bodily shed at the end of it, and the "gular pouch" in the throat of the breeding bustard, are examples of a more special kind, the existence of which, however, must be connected, either directly or indirectly, with the contemporaneous increase of sexual activity and the enhanced vitality which accompanies it.

With birds, however, the assumption of the most perfect male plumage is not necessarily synchronous with the period of enhanced vitality. Thus Grinnell[4] says that in the linnet "the brilliant hue of the nuptial dress" is acquired in August, or several weeks after the season of mating, instead of immediately preceding it, and so is not directly associated with excessive sexual vigour. There is only one moult annually and no pre-nuptial moult, but a progressive increase in coloration up to and beyond the breeding season.[1]

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[1] Numerous instances are given by Darwin, *loc. cit.*, both for fishes and Amphibians.

[2] The nuptial changes which occur in fishes are not necessarily in the direction of increased brilliance of coloration. Miss Newbigin describes these changes in the salmon as follows: "When the fish comes from the sea the skin is of a bright silvery hue, while the flesh has the familiar strong pink colour. The small ovaries are of a yellow-brown colour. As the reproductive organs develop during the passage up the river, certain definite colour-changes occur. The skin loses its bright silvery colour, and, more especially in the male, becomes a ruddy-brown hue. At the same time the flesh becomes paler and paler, and in the female the rapidly growing ovaries acquire a fine orange-red colour. The testes in the male remain a creamy white. After spawning the skin tends, in both sexes, to lose its ruddy colour and to regain the bright silvery tint; the flesh, however, remains pale until the kelt has revisited the sea" (*Report of Scottish Fishery Board*, 1898).

Barrett-Hamilton (*Proc. Camb. Phil. Soc.*, vol. x., 1900, and *Annals and Mag. of Nat. Hist.*, vol. ix., 1902) draws attention to many such sexual phenomena, and more especially to those occurring in the spawning season in certain salmonoid fishes of the genus *Onchorhynchus*. The fish undergo extraordinary changes in colour and shape, and, since they die when spawning is accomplished, it is argued that the changes cannot have any æsthetic significance, but represent a pathological condition in which the fish become continually more feeble and eventually succumb.

[3] Beebe ("Preliminary Report on an Investigation of the Seasonal Changes of Colour in Birds," *Amer. Nat.*, vol. xlii., 1908) describes an experiment in which certain tanagers and bobolinks, which had been prevented from breeding, were kept throughout the winter in a darkened chamber with a somewhat increased food-supply. As a consequence the nuptial plumage was retained until the spring, when the birds were returned to normal conditions. They shortly afterwards moulted. The breeding plumage was then renewed, so that in this case the dull winter plumage was never acquired.

[4] Grinnell, "Concerning Sexual Coloration," *Science*, vol. xxxiii., (Jan.) 1911.

In some animals certain glandular organs, apart from those concerned in the reproductive processes, show a special activity at the breeding season. For example, in the swiftlets (*Collocalia*) the salivary glands become peculiarly active, and secrete a substance which is allied to mucin, and is employed in building the edible birds' nests of Chinese epicures.[2]

A somewhat similar peculiarity exists in the male of the sea-stickleback (*Gasterosteus spinachia*), which binds together the weeds forming its nest by means of a whitish thread, secreted by the kidneys, and produced only during the breeding season. According to Möbius, as quoted by Geddes and Thomson,[3] the secretion is semi-pathological in nature, being caused by the mechanical pressure of the enlarged testes upon the kidneys. The male gets rid of the thread-like secretion by rubbing itself against objects, and thus, by an almost mechanical process, the weaving habit is supposed to have become evolved.

During the breeding season the anal scent-glands of snakes are said to be actively functional, but not at other times. A similar fact is stated about the submaxillary glands of crocodiles, and the cloacal glands of tortoises and other reptiles.[4] The secretions of these glands, like the musk glands of Mammals, no doubt serve the purpose of enabling the sexes to detect one another's presence more easily. (See p. 253.)

PERIODICITY

The periodicity which is such a marked feature of animal life in temperate climates has been discussed at some length by Semper.[5] This author concludes that the phenomenon in question is dependent on the severe extremes of summer and winter temperature to which the animals are exposed. "Every individual requires a certain duration of life to achieve its individual development from the egg to sexual maturity and full growth; the length of time requisite for this is very various, and, above all, bears no proportion to the size attained. . . . This length of time, which we may generally designate as the period of individual growth, is not alike even for all the individuals of the same species; on the contrary, it depends on the co-operation of so many different factors that it must necessarily vary considerably. Now, if from any cause the period of individual growth, say of the salmon, became changed in consequence of the slower development of the embryo in the egg or of the young larvæ, most or all the young salmon thus affected would die in our climate, because the greater heat of spring is injurious to them at that stage." In a similar way it may be argued that the periodicity of the breeding season, no less than the rate of growth, is governed by the necessities of the young. No doubt this is true to a large extent, yet at the same time it is equally evident, as has been shown above in numerous instances, that this periodicity is greatly affected by climatic and environmental changes, and even by stimuli of a more particular nature (*cf.* frogs, p. 19). But this power, which all animals in some degree possess, of responding to altered conditions, may none the less have arisen primarily to meet the requirements of the next generation; or, to speak more accurately, that those animals which breed at a certain particular season (or in response to certain conditions which prevail at that season) have the advantage in being able to produce a new generation to which this capacity to respond similarly will be transmitted. In other words, the restriction of the breeding habit to certain seasons may have been brought about under the influence of natural selection to meet the necessities of the offspring.[1]

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[1] The assumption of plumage by birds (ducks, bullfinches, etc.) in the autumn and long before the breeding season may be due to the time of moult. Patten has shown that in the sanderling there is a pre-nuptial plumage closely resembling the plumage of the sexually mature bird but preceding the enlargement of the gonads. ("The Vernal-Plumage Changes in the Adolescent Blackbird and their Correlation with Sexual Maturity," *Brit. Assoc. Report*, 1911.)

[2] Geddes and Thomson, *Evolution of Sex*, Revised Edition, London, 1901.

[3] Geddes and Thomson, *loc. cit.*

[4] Owen, *Anatomy of Vertebrates*, vol. i., London, 1866. Laycock, *Nervous Diseases of Women*, London, 1840.

[5] Semper, *Animal Life*, London, 1881.

Heape, however, has raised the objection[2] that this view is inapplicable to the Mammalia, in which there is a period of gestation of greatly varying length in the different species. If the theory were correct, why, he asks, do some bats experience a breeding season in the autumn, and not produce young until the following June, although only two months are required for the development of the embryo in

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[1] Westermarck (*The History of Human Marriage*, 5th Edition, London, 1921) says it is "obvious that the sexual functions are, at least to some extent, affected by different conditions in different species. This is shown by the fact that every month or season of the year is the pairing time of one or another species of Mammals." He goes on to cite examples. Moreover, he points out that while the Adélie penguin rears its young in the warmest and lightest months, the giant Emperor penguin does this in the dark season, so that they may be fostered by their parents until the warm weather, and have the whole summer in which to change their plumage (Levick, *Antarctic Penguins*, London, 1914). Westermarck points out also that where the conditions amid which certain animals live are fairly uniform throughout the year there is no sexual season. He instances the whale, the elephant, and the birds of the Galapagos Islands which are situated very near the equator. (*Cf.* p. 13.)

[2] Heape, "The Sexual Season of Mammals," *Quar. Jour. Micr. Science*, vol. xliv., 1900.

these animals; why do roe-deer in Germany breed in autumn, while the embryo does not develop beyond the segmentation stage until the following spring; and why does the seal take eleven or twelve months for gestation when a large dog requires only nine weeks? Heape believes that the recurrence of the breeding season is governed directly by climatic, individual, and maternal influences,[1] and that "variation in the rate of development of the embryo, in the length of gestation, and in the powers of nursing, are quite sufficient to provide for the launching of the young at a favourable time of the year."

I cannot altogether concur in Heape's view of this question. For it seems to me by no means improbable that whereas the necessities of the offspring, under changed environmental conditions, may sometimes have been provided for by modifications in the rate of development or length of gestation, yet in other cases a similar result may have been effected by alterations in the season of breeding. The mere fact that breeding in any one species occurs, as a rule, periodically at a time which is on the whole well suited to the requirements of perpetuating the race, is itself presumptive evidence that the periodicity of the breeding season is controlled (through natural selection) by the needs of the next generation. Further, the breeding season having been fixed at one period in the history of the species, the same season would probably be retained (in the absence of disturbing factors) by the descendants of that species under the directive influence of heredity. This view is in no way opposed to the doctrine that the sexual capacity is developed in the individual in response to definite stimuli, which are largely environmental and often seasonal.

The occurrence of a succession of "heat" periods within the limits of a single breeding season no doubt arose in consequence of the increased opportunity afforded thereby for successful copulation. The number and frequency of the "heat" periods under these circumstances are affected by the conditions under which an animal lives in just the same kind of way as the periodicity of the breeding season is affected, as will be shown in the succeeding chapter on the œstrous cycle in the Mammalia. Concerning the immediate cause of "heat," and the nature of the mechanism by which it is brought about, something will be said later (Chapter IX.).

The origin of the breeding season is a wider question. For its complete solution, as pointed out by Heape, a comparative study of the sexual phenomena in the lower animals is essential, while, as already remarked, sufficient data for a comprehensive treatment of this subject do not at present exist.

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[1] Under the heading of "individual influences" Heape includes special nervous, vascular, and secretory peculiarities of the individual and its habits of life. The length of the gestation and lactation periods he calls "maternal influences."

That the breeding season occurs in some animals "as the result of a stimulus which may be effected through the alimentary canal is demonstrated by the effect upon ewes of certain stimulating foods."

"That it is associated with a stimulus which is manifested by exceptional vigour and exceptional bodily 'condition' is demonstrated by the pugnacity of the males at such times, by the restless activity of the females, by the brilliant colouring of such widely divergent animals as, for instance, annelids, amphibia, birds, and mammals, by the condition of the plumage of birds, and of the pelage or skin of mammals."

"That it is [frequently] associated with nutrition, and that it is a stimulus gradually collected is indicated by the increased frequency of the [breeding] season among domesticated mammals as compared with nearly allied species in the wild state.

"That it is manifested by hypertrophy and by congestion of the mucous tissue of the generative organs, and of various other organs, such as the wattles and combs of birds, the crest of the newt, and by the activity of special glands, the affection of all of which may be exceedingly severe, is true.

"These, and many other similar facts, are well known, but they do not assist in the elucidation of the origin of the function.

"The most they do is to show that the sexual instinct is seasonal, and that nutrition, whether affected by external or internal factors, plays an important part in its manifestation." [1]

The last proposition may be expressed even more generally in the statement, already formulated, that generative activity in animals occurs only as a result of definite stimuli, which are partly external and partly internal; while the precise nature of the necessary stimuli varies considerably in the different kinds of animals, according to the species, and still more according to the group to which the species belong.[2]

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[1] Heape, *loc. cit.* It should be remembered, however, that many animals, such as the salmon, have their breeding season after prolonged fasts. See above. *Cf.* also the fur-seal, p. 54.

[2] For a number of illustrations of periodicity in generative activity among animals inhabiting the sea-shore, and the tendency to modify chapters of the normal life-history in accordance with special needs, or in response to peculiar environmental conditions, see Flattely and Walton, *The Biology of the Sea-Shore*, London, 1922.

CHAPTER II

THE ŒSTROUS CYCLE IN THE MAMMALIA

> "Omne adeo genus in terris hominumque ferarumque
> Et genus æquoreum, pecudes, pictæque volucres
> In furias ignemque ruunt : amor omnibus idem."
>
> —VIRGIL, *Georg.* iii.

IN describing the sexual processes of the Mammalia, and the variations in the periodicity of breeding which occur in the different groups, I have employed the terminology originally proposed by Heape,[1] and afterwards adopted by me,[2] in giving an account of these phenomena in the sheep and other animals. The terms used may now be defined.

The term *sexual season* is used by Heape to designate the particular time or times of the year at which the sexual organs exhibit a special activity. It is, in fact, employed in practically the same sense as that in which the expression "breeding season" is used in the previous chapter. Heape suggests that it is better to adopt the latter term to denote "the whole of that consecutive period during which any male or female mammal is concerned in the production of the young," since the expression is often used to include the period of pregnancy or even the period of lactation. The sexual season is the season during which copulation takes place, but this only occurs at certain still more restricted times, the periods of "œstrus" (defined below). The male sexual season, when there is one, is called the *rutting season*; but in many species the male animals are capable of copulating at any time, whereas in the females this function is restricted to definite periods.

The non-breeding season or period of rest in a female mammal, when the generative organs are quiescent (at least relatively) and the uterus is normal and comparatively anæmic, and the animal shows no disposition to seek out a mate, is called by Heape the *Anæstrous period* or simply the *Anæstrum*. This period is generally considerably prolonged, and in many Mammals occupies the greater part of the year. Its close marks the beginning of the sexual season.

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[1] Heape, "The Sexual Season," *Quar. Jour. Micr. Science*, vol. xliv., 1900.

[2] Marshall, "The Œstrous Cycle and the Formation of the Corpus Luteum in the Sheep," *Phil. Trans.*, B., vol. cxcvi., 1903. "The Œstrous Cycle in the Common Ferret," *Quar. Jour. Micr. Science*, vol. xlviii., 1904. See also Marshall and Jolly, "Contributions to the Physiology of Mammalian Reproduction: Part I. The Œstrous Cycle in the Dog," *Phil. Trans.*, B., vol. cxcviii., 1905.

The first part of the sexual season is occupied by the *Prœstrum.* This period is characterised by marked changes in the generative organs, the uterus becoming congested, while in the later stages there is often a flow of blood from the external opening of the vagina. The prœstrum is the period often referred to by breeders as the time when an animal is "coming on heat," or "coming in season."

The next period, *Œstrus*, or *Œstrum* (as it is sometimes called), "marks the climax of the process; it is the special period of desire in the female; it is during œstrus, and only at that time, that the female is willing to receive the male, and fruitful coition rendered possible in most, if not in all, mammals."[1]

The periods of prœstrum and œstrus are commonly referred to together as the "heat" or "brunst" period, and sometimes as the period of "rut,"[2] and no attempt is then made to distinguish the time occupied by "coming in season," and the time at which the female is ready to receive the male. This failure to distinguish the two periods (prœstrum and œstrus) has led to much confusion, especially in regard to the nature of the relation between "heat" in the lower Mammals and menstruation in the human female. As was first pointed out by Heape, it is the prœstrum and not the entire "heat" period which is the physiological homologue of menstruation. This is a point which will be dealt with more fully in the next chapter of this book.

If conception takes place as a result of coition during œstrus, this period is followed by gestation;[3] gestation in its turn, after a short puerperium or period of recovery, is followed by nursing or lactation, and the latter is succeeded by another anœstrum at the close of the breeding season.[4]

If, on the other hand, conception does not occur during œstrus, the latter is succeeded, either by a short *Metœstrum*, during which the activity of the generative system subsides and the organs gradually resume the normal condition (cat, rabbit), or by a period which may be called pseudo-pregnancy, in which the changes occurring in the sexual organs are in a general way similar to those which take place during true pregnancy but without being so pronounced (dog).[1] The pseudo-pregnant period is then followed by another anœstrum or period of prolonged rest.

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[1] Heape, *loc. cit.*

[2] The term "rut" is used by Heape in the case of the male only, the "rutting season," as stated above, being the male sexual season.

[3] There is evidence that "heat" may occur abnormally during gestation. This phenomenon has been observed in dogs, cows, horses, and other animals (see p. 46). Coition during pregnancy may result in superfœtation (see p. 154), and may tend to occur periodically at times corresponding to what would have been the regular heat periods if the animal had remained non-pregnant.

[4] In some animals parturition is followed almost immediately by another prœstrum and œstrus, in spite of lactation.

In some animals, such as the rat or the rabbit, the metœstrum may be succeeded by only a short interval of quiescence. This short interval, which sometimes lasts for only a few days, is called the *Diœstrum.* This in turn is followed by another procœstrous period, and so the cycle is repeated until the sexual season is over. Such a cycle (consisting of a succession of the four periods, procœstrum, œstrus, metœstrum, and diœstrum) is known as the Diœstrous cycle. The number of diœstrous cycles in one sexual season depends upon the occurrence or non-occurrence of successful coition during œstrus. Thus, if conception takes place during the first œstrous period of the season, there can be no repetition of the cycle, at any rate until after parturition. The cycle may then be repeated. If conception does not occur at any œstrus during the sexual season, the final metœstrous period is succeeded by a prolonged anœstrous or non-breeding period. This is eventually followed by another procœstrum, marking the commencement of a new sexual season. The complete cycle of events is called the Œstrous cycle.

The number of diœstrous cycles which can occur in a female mammal in the absence of the male, or in the absence of successful coition, depends upon specific and individual differences. Thus in some animals, such as the Scotch blackfaced sheep in the Highlands, this number is usually limited to two. In many Rodents, on the other hand, there may be six or seven, or even more recurrences of the cycle within the limits of a single sexual season.

Animals in which the œstrus does not recur during the sexual season, Heape has called Monœstrous animals. Those in which there is a recurrence of the diœstrous cycle during a single season, have been designated Polyœstrous animals. The polyœstrous condition may be regarded as a device (using teleological language) to increase the reproductive powers by providing more frequent opportunities for successful coition. But as to what factors are actually involved in bringing about the rhythmic recurrence of the cycle is a question which must at present be left open. (*Cf.* p. 387.)

The differences in sexual periodicity in both monœstrous and polyœstrous Mammals, the differences in the duration of the sexual season in polyœstrous Mammals, the great variation which occurs even in closely allied forms or even within the limits of a single species, and the effects of domestication and climate upon sexual and reproductive capacity are points which will be considered in describing the various types of breeding phenomena which exist in the different groups.

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[1] Marshall and Halnan, "On the Post-Œstrous Changes occurring in the Generative Organs and Mammary Glands of the Non-Pregnant Dog," *Proc. Roy. Soc.*, B., vol. lxxxix., 1917.

As Heape says, "the complication into which an otherwise simple story is thrown is due . . . to variation in the quiescent period." The two varieties of the quiescent period (anœstrum and diœstrum) "are homologous, the one is a modification of the other"; and the modification is no doubt related to an increased or decreased power of reproduction. At the same time, for the purposes of the present chapter, "the difference between them [must be regarded as] essential, for their relation to the sexual season renders it necessary to discriminate clearly between them."

MONOTREMATA

Little is known concerning the breeding habits of the platypus and the echidna, which represent this order, the lowest of the Mammalia. Semon[1] states that they breed only once a year, and that in *Echidna*, as a general rule, only a single egg is impregnated and developed at a time. After the egg is laid (for Monotremes, as is well known, differ from all other Mammals in being oviparous) the mother stows it away in her pouch. This is always well developed at the sexual season, after which it disappears, not to appear again until the approach of the next sexual season. Semon states that, although the pouch is first visible in the embryo, it is thereafter lost to sight until the beginning of the first proœstrum.

MARSUPIALIA

It would appear probable that most Marsupials breed once annually, but some are said to do so more frequently. Semon[2] says that in the native Australian "bear" (*Phascolarctus cinereus*), on the Burnett, the sexual season begins at the end of October. Since he failed to find pregnant females until the middle or end of November, it would seem that the sexual season probably extends for three or four weeks. The males at this time experience a rutting season, during which they cry loudly, more frequently in the evening and night, but also during the day. The gestation, as in all

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[1] Semon, *In the Australian Bush*, English Edition, London, 1899. See also Sixta, "Wie junge Ornithorhynchi die Milch ihrer Mutter saugen," *Zool. Anz.*, vol. xxii., 1899; and Caldwell, "The Embryology of Montremata and Marsupialia," *Phil. Trans.*, B., vol. clxxviii.

[2] Semon, *loc. cit.*

Marsupials, is extremely short, the young being transferred at a very early stage of development to the mother's pouch, as in the case of *Echidna*.[1]

The kangaroos in the Zoological Society's Gardens in London are stated to display sexual excitement in September, and also in April. At such times a slight flow of mucus, which may be tinged with a little blood, has been observed passing from the aperture of the vagina.[2] It would appear, therefore, that kangaroos may breed twice a year. Unfortunately, there is no positive information available as to whether œstrus recurs during the same sexual season (see below).

The Marsupial cat (*Dasyurus viverrinus*) is monœstrous and has one breeding season a year, which begins in May or early June and extends over the winter in Australia, until the first fortnight in August.[3] The prTouchœstrum lasts from four to twelve days, and during this time the lips of the cloaca become swollen, and the pouch enlarges slightly and becomes tumid and moist. There are corresponding internal changes (see below, p. 106). Œstrus lasts for one or two days. Pregnancy is stated to last not less than eight and not more than fourteen days. In its absence pseudo-pregnancy occurs, and is accompanied by a series of changes in the reproductive organs and mammary glands essentially similar to those taking place in gestation. The pouch enlarges and the sebaceous, sweat, and mammary glands also hypertrophy as well as the internal organs (see p. 616). At the end of the period the animal has been seen to clean out its pouch for the reception of young, showing that the developmental and cyclical changes of the sexual organs may extend even to the instincts associated with parturition and the nursing of the young, although true pregnancy had not taken place (*cf.* rabbit, p. 576). The anœstrum in *Dasyurus* lasts more than half the year.

Hill states that the opossum (*Didelphys aurita*) has two breeding seasons; one in June to July, and the other at the end of October. The Virginian opossum, on the other hand, has only one sexual season and one œstrus. *Trichosurus vulpecula* and *Macropus ruficollis* breed twice a year, the former in April and September, the latter in August to September and December to February.[4]

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[1] In the bandicoot (*Perameles*) the young are nourished by an allantoic placenta similar to that of the higher Mammals (see p. 419). This is exceptional among Marsupials.

[2] Wiltshire, "The Comparative Physiology of Menstruation," *Brit. Med. Jour.*, 1883.

[3] Hill and O'Donoghue, "The Reproductive Cycle in the Marsupial *Dasyurus viverrinus*," *Quar. Jour. Micr. Science*, vol. lix., 1913.

[4] Hill, "Some Observations on the Early Development of *Didelphys aurita*" (Contributions to the Embryology of the Marsupialia, V.), *Quar. Jour. Micr. Science*, vol. lxiii., 1918. See also below, p. 106.

RODENTIA

There can be little doubt that the great majority of Rodents are polyœstrous. Most of them, so far as is known, have one annual breeding season, which may, under favourable conditions, extend over several months. Thus the rat (*Mus decumanus*) and mouse (*M. musculus*) are known to experience a recurrence of the diœstrous cycle in the absence of the male, while, if pregnancy occurs, a new "heat" period very rapidly succeeds parturition. In a state of semi-domestication *M. rattus* and *M. decumanus* have, in my experience, a fairly regular breeding season from about the end of January until the end of May. During this period the majority of mature females are either pregnant or suckling their young (that is, of course, among females which have been allowed to run freely with males). Pregnancy may occur at other times of the year, but is not nearly so common. The duration of the diœstrous cycle in the rat is said to be about five days,[1] but observers seem to differ, some stating it to be longer; the period of gestation is approximately three weeks. Heape states that *M. minutus* and *M. sylvaticus* are also probably polyœstrous. The bank vole (*Arvicola glareolus*) is almost certainly polyœstrous, since it can become pregnant immediately after parturition at certain times of the year. The same condition no doubt exists in the field vole (*A. agrestis*), which breeds in Britain from January to October.[2] According to Lataste,[3] *Eliomys quercinus*, *Gerbillus hertipes*, *Dipodillus campestris*, *D. simoni*, *Meriones shawi*, and *M. longifrons* are also polyœstrous. The length of the diœstrous cycle in all these animals, as observed by the same investigator, is usually about ten days.

In the wild condition in Britain, according to Heape, recurrent diœstrous cycles last "about three months, probably, in *Arvicola agrestis*; from four to six months, probably, in *Mus minutus*; about nine months in *Mus rattus*; and even longer, perhaps, in *Mus musculus* and *M. decumanus*." From my own experience with the two species of rats in captivity, I am disposed to believe that Heape has overstated the duration of the sexual season in these animals in a state of nature.

The breeding season in the wild rabbit (*Lepus cuniculus*) in this country generally lasts from about February to May, but may be continued for longer. In the domesticated breeds it sometimes lasts nearly the whole year if the circumstances be favourable in regard to warmth and food supply. Heape says that five or six months only is the usual duration of the period during which diœstrous cycles recur in the domestic rabbit, and that if œstrus is experienced in winter it may occur independently of the possibility of pregnancy.

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[1] Long and Evans, "The Œstrous Cycle in the Rat," *Anat. Rec.*, vol. xviii., 1920.

[2] Millais, *British Mammals*, vol. ii., London, 1905.

[3] Lataste, *Recherches de Zoöthique sur les Mammifères de l'ordre des Rongeurs*, Bordeaux, 1887.

The duration of the diœstrous cycle varies considerably. "While some individuals exhibit œstrus every three weeks fairly regularly, others do so every ten days; on the whole, I think ten to fifteen days is the usual length of their diœstrous cycle."[1] In *Lepus variabilis* recurrent diœstrous cycles are probably continued for about two months.[2]

The squirrel (*Sciurus vulgaris*) in Britain, according to Heape, is probably monœstrous; but this animal, in Southern Europe and Algiers, according to Lataste, is apparently polyœstrous. In Britain squirrels breed early in the year, and sometimes have a second litter in August.

It is difficult to determine the length of the proœstrum and œstrus in Rodents, since the external changes which characterise these conditions are comparatively slight. Heape says that the proœstrum in the rabbit lasts, probably, from one to four days. At this time the vulva tends to become swollen and purple in colour, but there is no external bleeding. According to Long and Evans[3] the cycle is marked by characteristic changes in the cellular and fluid content of the vagina. Lataste[4] states that external bleeding occurs during the "heat" periods of *Pachyuromys duprasi*, *Dipodillus simoni*, and *Meriones shawi*.

The guinea-pig (*Cavia porcellus*) in captivity can become pregnant at any season, but more frequently in the summer than in the winter. Stockard and Papanicolaou[5] state that œstrus occurs every sixteen days and that the vagina just before these periods becomes filled with mucus. During the diœstrum there is very little fluid to be found in the vagina.

Loeb[6] had previously found that the diœstrous cycle lasted from twenty to twenty-five days, or in animals prevented from copulating, from fifteen to nineteen days. "Heat" rapidly succeeds parturition, as in the case of so many other Rodents.[7] The period of gestation is about sixty-two days, an unusually long time for so small an animal, being more than twice as long as the gestation period of the rabbit. As a result the newly-born guinea-pig is well advanced in development, and able to feed for itself, instead of being dependent on its mother's milk.

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[1] Heape, *loc. cit.*

[2] The diœstrous cycles may be interrupted by a period of pseudo-pregnancy initiated by a sterile coition. See below, p. 101.

[3] Long and Evans, *loc. cit.*

[4] Lataste, *loc. cit.*

[5] Stockard and Papanicolaou, "The Existence of a Typical Œstrous Cycle in the Guinea-Pig," *Amer. Jour. Anat.*, vol. xxii., 1917.

[6] Loeb, "The Cycle Changes in the Ovary of the Guinea-Pig," *Jour. of Morph.*, vol. xxii., 1911. "The Correlation between the Cyclic Changes in the Uterus and the Ovaries," *Biol. Bull.*, vol. xxvii., 1914.

[7] Sobotta, "Über die Bildung des Corpus Luteum beim Meerschweinchen," *Anat. Hefte*, vol. xxxii., 1906.

In most male Rodents the testes undergo a periodic increase in size and descend into the sessile scrotum at the beginning of the season of rut, after which they become smaller again, and are withdrawn into the peritoneal cavity. In the Leporidæ, however, and in some other species, the testes are not so retracted, but remain throughout the year in the scrotal sacs.[1]

UNGULATA

This order contains several examples of animals which are almost certainly monœstrous in a state of nature, but are polyœstrous in captivity or under domestication. In the latter case the increase in sexual capacity appears to be due partly to the inherited effects of domestication, and partly to the direct influence of a more favourable environment.

For example, the sheep presents a complete gradation from the apparently monœstrous condition of some wild species to the extreme degree of polyœstrum, which is reached by certain of the more domesticated breeds.[2]

The Barbary wild sheep (*Ovis tragelaphus*) in the Zoological Society's Gardens is monœstrous, breeding only once annually.[3] The same is stated to be the case with the Burrhel sheep (*O. burrhel*), although the moufflon (*O. musimon*) in captivity may experience two or more recurrent diœstrous cycles in an annual sexual season.[4] It would seem, however, from the account given by Lydekker[5] of the breeding habits of *O. musimon*, as well as *O. vignei*, *O. ammon*, and *O. canadensis*, that these sheep in their wild condition are probably monœstrous, for their annual sexual season is of short duration, and occurs with great regularity. Similarly it may be inferred from Prjewalsky's statements[6] that *O. poli*, *O. burrhel*, and *O. argali* are monœstrous and breed once a year. Among wild sheep generally the sexual season occurs as a rule in autumn, but it may vary with the locality or climate. Thus with *O. vignei* in the Punjab, the sheep begin to breed in September, whereas, with the same species in Astor, the sexual season must be considerably later, since the young in the latter district are produced about the beginning of June.[1]

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[1] Owen, *On the Anatomy of Vertebrates*, vol. iii., London, 1868.

[2] Marshall, "The Œstrous Cycle, etc., in the Sheep," *Phil. Trans.*, B., vol. cxcvi., 1903.

[3] Heape, *loc. cit.*

[4] I am indebted to Mr. F. E. Beddard, Prosector of the Zoological Society, for this information.

[5] Lydekker, *Wild Oxen, Sheep, and Goats of All Lands*, London, 1898.

[6] Prjewalsky, *Mongolia, the Tangut Country, and the Solitudes of Northern Tibet* (Morgan's Translation), London, 1876.

Scotch Blackfaced sheep in the Highlands experience two diœstrous cycles, each of three weeks' duration, so that the annual sexual season for these animals lasts six weeks. In the Lowlands the sheep of this breed may have at least three recurrent diœstrous cycles in the absence of the ram, while flockmasters inform me that, under unusually favourable conditions, there may be as many as five or six, the duration of each cycle varying from about thirteen to eighteen days. It can hardly be doubted that of the two conditions of the Scotch Blackfaced sheep that of the Highland ewes is the more natural, for sheep, in their wild state, are essentially mountain animals, being almost entirely confined to mountain districts in the Holarctic region, their range only just extending across the border into the far warmer Oriental region. "The immense mountain ranges of Central Asia, the Pamir, and Thian-Shan of Turkestan may be looked upon as the centre of their habitat."[2]

The sexual season in hill sheep in Great Britain is ordinarily from about the middle of November until the end of the year. Under exceptional circumstances individuals may experience œstrus at other seasons, such as in April after an early abortion in the winter. In other British breeds the sexual season is earlier. Thus Hampshire Down sheep are often "tupped" in the summer, but they do not, as a rule, breed more than once a year. The Limestone sheep of Westmorland and Derbyshire, and the Dorset Horn sheep of the South of England, are the only British sheep which are ordinarily capable of breeding more than once annually. With the former the general lambing season is from the middle of February to the middle of March, but lambs are often born earlier. The ewes sometimes receive the ram very early when suckling the lambs, so that a second crop of lambs is born in August. This increase in the sexual capacity is especially noteworthy in view of the fact that Limestone sheep are classed as a mountain breed which thrives best on dry heaths or bare hill pastures. In Dorset Horn sheep lambs are frequently produced twice a year, but the practice is discouraged as it is said to deteriorate the ewes. With this breed œstrus may continue to recur (in the absence of the ram) from the summer sexual season (when the sheep are tupped) onwards until the late autumn or even longer.

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[1] Lydekker, *loc. cit.*

[2] Flower and Lydekker, *Mammals Living and Extinct*, London, 1891.

With many foreign breeds lambs are born twice yearly. Thus Dr. Annandale informs me that the horned sheep which run half wild in Patani, in the Malay Peninsula, normally have lambs twice a year. It would appear also that among the indigenous sheep of India, which are scarcely ever supplied with any artificial or other food, green or dry, beyond what they can pick up at the pasture ground, lambs may be born three times in two years, and that there are no definite seasons for lambing.[1]

Among the Merino sheep in Cape Colony the sexual season is April (the autumn month, corresponding to October in this country), but some sheep come "in season" earlier. At high altitudes, however, where the sheep subsist entirely upon the natural produce of the veldt, the sexual season is May, or a month later than the usual time in Cape Colony. On the other hand, in the low country below the second range of mountains, there are two seasons for "tupping," and lambs are produced twice a year. Among the Merinos in Argentina there are also two breeding seasons within the year.

Probably the maximum amount of sexual activity experienced by any sheep is that reached by certain Australian Merinos which are described as being able to breed all the year round, a fact which implies, in the absence of gestation, an unbroken series of diœstrous cycles. The report of the Chief Inspector of Stock for New South Wales divides the time of lambing into six periods which embrace the entire year.[2]

That the great variability in sexual activity which the sheep exhibits is dependent largely upon differences in food supply and climate cannot be doubted, for the Blackfaced sheep in Scotland and the Merinos in Cape Colony afford direct evidence that this is the case. Indeed, the effect of the environment on the recurrence of breeding was noted long ago by Aristotle,[3] who observes that "in some places where the weather is warm and fine, and food is abundant," sheep may have lambs twice a year. The result of flushing (or the practice of stimulating the generative system by supplying extra food or better pasture, and thereby hastening the approach of the sexual season and increasing the fertility) is further evidence of the effect of good nourishment upon the sexual and reproductive powers. On the other hand, there can be no question that the varying degrees of breeding activity are in part racial characteristics, as is shown, for example, by the Dorset Horn sheep in the South of England, and still more evidently by the Limestone sheep of Westmorland and Derbyshire. But that an increase in the duration (or more frequent recurrence) of the sexual season is not necessarily a highly artificial condition or the result of special attention in regard to food supply, etc., on the part of the flock-master, is shown by such a condition occurring among the indigenous sheep of India and the half-wild sheep of Patani.

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[1] Shortt, *A Manual of Indian Cattle and Sheep*, 3rd Edition, Madras, 1889.

[2] Wallace (R.), *Farming Industries of Cape Colony*, London, 1876; *The Rural Economy and Agriculture of Australia and New Zealand*, London, 1891; *Argentine Shows and Live Stock*, Edinburgh, 1904.

[3] Aristotle, *History of Animals* (Cresswell's Translation), Bohn's Library, London, 1862. Oxford Edition (Thompson's), 1910.

The duration of the diœstrous cycle in Blackfaced sheep, as already mentioned, is from about thirteen to twenty-one days, the variation appearing to depend partly upon the nature of the country in which they live. In other breeds the cycle may be said to vary within approximately the same limits. Ellenberger,[1] however, gives from twenty to thirty days as the length of this interval. The proœstrum and œstrus together do not as a rule occupy more than two or three days, and œstrus alone may last for only a few hours. The external signs of the proœstrum are comparatively slight in sheep.[2] The vulva is usually somewhat congested, and there is often a flow of mucus from the external generative aperture, but blood is seldom seen. Owing to the extreme shortness of the "heat" period the mucous flow may continue during the œstrous and metœstrous periods. The internal changes are briefly described in the succeeding chapter. The only external indication of œstrus is that afforded by the behaviour of the ewes. At this time they tend to follow the ram, and display a general restlessness of demeanour. The period of gestation is twenty-one or twenty-two weeks. Nathusius' observations show that it is fairly constant within the limits of particular breeds.[3]

The œstrous cycle in the sheep, and its great variability, have been discussed at some length, since this animal is probably typical of most Ungulata in the way in which its generative system is affected by different conditions of life, while the facts about other Ungulates are not so perfectly known. The effect of changed conditions upon the sheep's fertility, *i.e.* upon its capacity to bear young (as distinguished from mere sexual capacity), is a subject which is dealt with more fully in a future chapter (Chapter XIV.).

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[1] Ellenberger, *Vergleichende Physiologie der Haussaügethiere*, vol. ii., Berlin, 1892.

[2] It is interesting to note that Aristotle clearly distinguished between the proœstrum and œstrus in the sheep and goat. This is what he says: "With ewes and she-goats there are signs of menstruation in breeding time, just before the time for submitting to the male; after copulation also the signs are manifest, and then cease for an interval until the period of parturition arrives" (Thompson's Translation, *loc. cit.*). The "signs after copulation" doubtless refers to vaginal bleeding, such as has been observed by Mr. Hammond in cows at such a time.

[3] Nathusius, "Ueber einen auffallenden Racenunterschied in der Trächtigkeitsdauer der Schafe," *Zool. Garten*, Jahrg. 3, 1862. (*Cf.* p. 68.)

The wild goat, like the wild sheep, has a very restricted sexual season,[1] while, according to Low, the domesticated goat experiences œstrus at very frequent periods.[2]

A similar statement may be made about cattle, for Heape[3] says that whereas wild cattle in captivity are capable of reproduction at any time of the year, and experience a remarkable increase in the recurrence of their diœstrous cycles, we are led to infer from the limited calving season among similar animals in the wild state that the sexual periods are likewise restricted. Raciborsky[4] says that in the more domestic types of cattle the cows receive the bull more frequently than in the wilder breeds. Ellenberger[5] states that among domestic cattle the diœstrous cycle varies from about two to four weeks, but Schmidt[6] has shown that the differences may be much greater. Wallace[7] says that œstrus recurs in summer every nineteenth day, but in winter it may not recur oftener than every twentieth or every twenty-first day. Usually the cow seeks the bull again four or five weeks after calving. Shortt,[8] however, states that in India this does not occur until after six or nine months. Blood is not infrequent in the external discharge of cows and heifers, but such discharge does not usually appear until after œstrus is over. Emrys-Roberts[9] has described the internal generative organs of a proœstrous cow as containing a watery secretion tinged with blood. The secretion was found to contain far less mucin than during the anœstrous period.[10]

The period of gestation in cattle is about nine months, but it is slightly variable.

According to Heape, who has collected evidence from various authorities, the ibex, markhor, barasingha, and *Hemitragus jerulaicus* in Cashmir, as well as the American bison, black-tailed deer in Montana, red-deer, fallow-deer, and roe-deer,[11] and several antelopes are all probably monœstrous in the wild state. This is rendered not unlikely from the limited sexual and calving seasons which these animals are known to experience, but it is by no means certain. "The American bison experiences a sexual season from some time in July until some time in August. [Catlin says August and September are the months when they breed; see below.] In the Cashmir ibex it persists during parts of November and December. In the markhor and *Hemitragus jerulaicus* in Cashmir it occurs in December, while in the barasingha in that country, from 20th September to 20th November, it has been observed. . . . In Scotland the red-deer's sexual season lasts three weeks, during September and October, according to Cameron;[1] while in this country [England] September is the sexual month for the fallow-deer,[2] and July and August the time when the roe-deer will receive the male.

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[1] Lydekker, *loc. cit.*

[2] Low, *The Domesticated Animals*, London, 1845.

[3] Heape, *loc. cit.*

[4] Raciborsky, *Traité de Menstruation*, Paris.

[5] Ellenberger, *loc. cit.*

[6] Schmidt, "Beiträge zur Physiologie der Brunst beim Rinde," *Dissertation, Zürich*, München, 1902.

[7] Wallace (R.), *loc. cit.*

[8] Shortt, *A Manual of Indian Cattle and Sheep*, 3rd Edition, Madras, 1889.

[9] Emrys-Roberts, "A Further Note on the Nutrition of the Early Embryo, etc.," *Proc. Roy. Soc.*, B., vol. lxxx., 1908.

[10] According to Emrys-Roberts, the profuse mucinous secretion during the proœstrum in the Mammalia is derived, not from the body of the uterus, but from the cervix and vagina.

[11] There has been some controversy regarding the breeding season and period of gestation in roe-deer. According to Bischoff (*Entwicklungsgeschichte*

"In all these cases there can be little over three weeks during which copulation takes place, and the extremely limited period during which parturition occurs strongly corroborates the view that this is the extent of the usual time during which sexual intercourse is possible. The fact that in captivity three weeks is the usual period which intervenes between two œstri in such animals, and the extreme probability that individual females do not experience œstrus at exactly the same time, predispose one to believe that they are monœstrous in the wild state; but, if the limit of time for coition is three weeks, there is still just time for the females to undergo two diœstrous cycles, and it is this possibility which prevents positive assertion on the matter.

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des Rehes, Giessen, 1854) rut occurs in early autumn, but the embryo is not developed beyond the stage of segmentation in the following spring. Grohmann (*Sport in the Alps*, Edinburgh, 1904) says that rut is experienced in July and the beginning of August, but that there is a "false rut" in November. Observations on roe-deer in Vienna showed that the period of gestation is ten months; for seven females which were served by one buck in July 1862 gave birth each to two young in the following May. It would appear probable, therefore, that the ovum lies dormant during the early months of gestation. Grohmann suggests that the "false rut" in November may have a quickening influence on the ovum, and so cause it to develop.

[1] Millais says (vol. iii., 1906) that the actual time of rut depends much on the season. September 28, in Scotland, is called "the day of roaring." Sir S. M. Wilson (*Field*, October 8, 1904), however, reports a case of a stag which roared during the whole summer in Kinveachy Forest, Boat of Garten, in 1904. Stags eat little or nothing during the rutting season, and lose weight rapidly. During the first days of roaring they are said to suck up a mixture of peat and water (Millais, *loc. cit.*).

[2] Millais says (*loc. cit.*) that the fallow-deer in England ruts in October. The necks of the big bucks swell greatly during the first week, and the animals become more and more unsettled until about the 25th, when the first calls are heard. The actual rut is short as a rule. The doe drops her calf about the beginning of June, and rarely two or three are born at a time. Sometimes, however, the females may come in season at irregular times, and drop calves in any of the months after June and even as late as November.

"Among captive animals, not more than two diœstrous cycles have been observed in the gnu during one sexual season. *Gazella dorcas* has two or three; the giraffe about three; while the eland, nylghau, and water-buck have a series of diœstrous cycles, each lasting three weeks, during May, June, and July each year.

"The gayal and bison, the axis and wapiti deer, on the other hand, experience a continuous series of diœstrous cycles all the year round, at intervals of about three weeks."[1]

Heape states also that with red-deer in the Zoological Gardens there is a very extensive series of diœstrous cycles, and that with wapiti deer in captivity the possibility of pregnancy at any season is only prevented by the fact that the male does not rut during the casting and growth of the antlers.

The males of many of the other species referred to experience a definite rutting season, like the stag in Britain.

As already mentioned, the male camels in the Zoological Gardens in London experience rut in early spring, or at the same time as the sexual season of the female camels in Mongolia.[2] The period of gestation in the camel is thirteen months, so that in this animal, as in the walrus among carnivores, the recurrence of the sexual season is delayed by pregnancy, and conception cannot take place oftener than once in two years.[3] The same is the case with the wild yak in the deserts of Tibet,[4] and also, in all probability, with the musk-ox in Greenland.[5]

The sexual season in many Ruminants is a period of intense excitement, especially in those cases in which the males experience a definite rut. (See above, p. 24, in Chapter I.) Thus, Catlin,[6] referring to the American bisons, says: "The *running season*, which is in August and September, is the time when they congregate into such masses in some places as literally to blacken the prairies for miles together. It is no uncommon thing at this season, at these gatherings, to see several thousands in a mass, eddying and wheeling about under a cloud of dust, which is raised by the bulls as they are pawing in the dirt or engaged in desperate combats, as they constantly are, plunging and butting at each other in the most furious manner. In these scenes, the males are continually following the females, and the whole mass are in a constant motion; and all bellowing (or 'roaring') in deep and hollow sounds which, mingled together, seem, at the distance of a mile or two, like the noise of distant thunder."

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[1] Heape, *loc. cit.*

[2] According to Sven Hedin (*Central Asia and Tibet*, London, 1903) the wild camels have a sexual season in December, January, and February, a fact which suggests that they are polyœstrous.

[3] Swayne, *Seventeen Trips through Somaliland*, London, 1895.

[4] Prjewalsky, *loc. cit.*

[5] Lydekker, *loc. cit.*

[6] Catlin, *North American Indians*, vol. i., 2nd Edition, London, 1841.

That the antlers are the fighting weapons in stags, and that their growth is associated with the advent of the sexual season, after which time they are cast off, are facts which have been already referred to. The effects of castration upon the growth of the antlers are described in a later chapter (p. 321).

Passing to the non-ruminating Ungulata, we find that the wild sow has only one annual sexual season. It is not certain whether this consists of more than a single œstrous cycle. Under domestication, however, the sow is polyœstrous, and may take the boar five weeks after parturition. The duration of the diœstrous cycle is from two to four weeks, according to Fleming.[1] The period of gestation is about four months. Litters are usually produced only in spring and autumn,[2] but by weaning the young early (or partially weaning them), and feeding the mother liberally, it is possible to get five litters in two years. A sanguineo-mucous flow has been observed issuing from the genital aperture during the procœstrum. At the same time the vulva is distinctly swollen.

Wiltshire[3] states that in the hippopotamus in captivity a condition of œstrus may be experienced at regular monthly intervals. This animal has been known to breed in Zoological Gardens.

The mare is polyœstrous, the normal diœstrous cycle being about three weeks and the œstrous period a week, though its actual length may vary by three or four days.[4] The sexual season in the absence of the stallion extends throughout the spring and early summer months, and is generally longest in the more domesticated breeds. Professor Ewart informs me that in a pony imported from Timor, which is in the Southern Hemisphere, œstrus was experienced in the autumn, or at the same time as the spring in Timor (*cf.* camels, p. 45). The period of gestation in the mare is eleven months, and "heat" recurs eleven days after parturition. This is called the "foal heat." Certain mares are irregular in the recurrence of the "heat" periods, and, in some, "foal heat" does not occur until seventeen days after parturition instead of the usual eleven days. In exceptional cases a mare, like a cow, may conceive at the "foal heat" and yet take the horse three weeks later, just as though she had failed to become pregnant.[1] Heape states that, very exceptionally, mares are monœstrous. Blood has been observed in the mare's proœstrous discharge, but it is not generally present. The genitalia, however, are always swollen and congested, and a glutinous secretion is generally emitted from them. The clitoris and vulva often undergo a succession of spasmodic movements, preceded by the discharge of small quantities of urine. Suckling mares tend to fail in their milk supply, and the quality of the milk appears to undergo some kind of change, as it is frequently the case that foals during the heat periods of their dams suffer from relaxation of the bowels or even acute diarrhœa. In mares which are not suckling the mammary gland becomes congested and increases in size during the heat. At the same time some mares develop great excitability, and kick and squeal, becoming dangerous to approach and impossible to drive. There is, however, great variation, for other animals may pass through the "heat" period without exhibiting any well-marked signs of their condition, which in a few instances can only be determined by the behaviour of the mare towards the stallion.[2]

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[1] Fleming, *Veterinary Obstetrics*, London, 1878.

[2] The times of breeding may be altered by farm practice. See Pearl, "The Seasonal Distribution of Swine Breeding," *Scientific Monthly*, September 1918. The diœstrous cycle is usually three weeks.

[3] Wiltshire, *loc. cit.* See also Ellenberger, *loc. cit.*, and Wallace (R.), *Farm Live Stock of Great Britain*, 4th Edition, London, 1907.

[4] Ewart found that in *Equus prjewalskii*, œstrus lasted a week.

The elephant in captivity is said to be polyœstrous, but I can find no record of the duration of the diœstrous cycle. Since pregnancy is very prolonged (twenty months), the sexual season cannot occur more than once in two years; that is, if the animals breed. The elephant in the Zoological Gardens in London is stated to have persistent œstrus probably for three or four days.

CETACEA

Little is definitely known about the periodicity of breeding in Cetacea. According to Millais,[3] the right whale brings forth in March in every other year, the young being suckled for about twelve months. The humpbacked whales, blue whales, and sperm whales appear to have no regular time for breeding, but Millais says the young of the humpbacked whales are generally born some time during the summer. Haldane's records,[1] which appear to refer to several different whales, show that fœtuses varying in length from six inches to sixteen feet were found in animals captured at the Scottish whaling stations in the summer of 1904. This great variation seems to imply that there is no regular season at which whales copulate, and that very possibly these animals are polyœstrous. Lillie[2] states that two specimens of *Balænoptera musculus* were taken off the west of Ireland on 31st July 1909, and that one contained a fœtus of one foot in length, while the other had a fœtus of five and a half feet in length. Lillie says also that several female rorquals having fœtuses of different sizes were captured within a short time of one another. These observations, therefore, are in a general way confirmatory of those of Haldane.

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[1] Wallace, *loc. cit.* Professor Ewart informs me that pregnant mares do not necessarily abort as a result of taking the horse at the third, sixth, or even ninth week of gestation.

[2] Wortley Axe, "The Mare and the Foal," *Jour. of the Royal Agric. Soc.*, 3rd Series, vol. ix., 1898. Ewart ("Studies on the Development of the Horse," *Trans. Roy. Soc. Edin.*, vol. li., 1915) says that the period of œstrus in mares tends to be shorter the later in the season, and when the food becomes less plentiful and less nutritious all external signs of œstrus disappear. Under favourable conditions, however, mares may become pregnant in winter. Ewart gives the following as the periods of gestation in various Equidæ :—Asses and zebras, 358 to 385 days; Prjewalsky's horse, 356 to 359 days; Celtic pony, 334 to 338 days. In coarse-headed types of horse it is about the same as in Prjewalsky's horse, but in the finer breeds the period is the same as in the Celtic pony. In abnormal cases pregnancy may be unduly prolonged in mares as in other animals, a mare occasionally going twelve months in foal instead of eleven.

[3] Millais, *The Mammals of Great Britain*, vol. iii., London, 1906.

According to Guldberg and Nansen,[3] the porpoise copulates at any time between June and October, the period of gestation being ten months or longer. Meek[4] states that the testes enlarge enormously in summer. The white-sided dolphin is said to copulate in late summer, pregnancy being about ten months, and the white-beaked dolphin is thought to be similar.[5]

Humpbacked whales and other Cetacea have been described as indulging in amorous antics at the breeding time, rubbing against one another and patting one another with their long fins.

CARNIVORA

In the female of the dog the average duration of the complete œstrous cycle is six months, there being two annual "heat" periods, typically in the spring and in the autumn. It follows, therefore, that the bitch is monœstrous. Bitches belonging to the smaller breeds tend to come "on heat" more frequently than those of the larger varieties. Thus, in Irish terriers, the cycle may recur after four months, though in this breed six months is the more ordinary time.[6] On the other hand, in Great Danes the duration of the œstrous cycle is often as much as eight months. It would appear that in those cases where "heat" recurs as often as every four months, this is only when pregnancy is prevented, for more than two litters of pups are seldom if ever produced in a year. Stonehenge[1] says that there is much individual variability in the periodicity of the cycle, and that "heat" may recur at any interval from four up to eleven months, but that six, five, and four months are the most usual periods. Each bitch as a rule has her own peculiar period to which she remains constant, unless systematically prevented from breeding, in which case the periods tend to recur irregularly or even cease altogether.[2] It has been observed also that the recurrence of the sexual season tends to become irregular with advancing age, and this irrespectively of whether or not the animal is permitted to become pregnant. The periodicity depends also to some extent upon climate, for in Danish Greenland the dogs usually breed only once a year.[3]

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[1] Haldane, "Whaling, etc.," *Annals of Scottish Nat. Hist.*, April 1905.

[2] Lillie (D. G.), "Observations on the Anatomy and General Biology of some Members of the larger Cetacea," *Proc. Zool. Soc.*, 1910.

[3] Guldberg and Nansen, *On the Structure and Development of the Whale*, Bergen, 1904.

[4] Meek, "The Reproductive Organs of the Cetacea," *Jour. of Anat.*, vol. lii., 1918.

[5] Millais, *loc. cit.*

[6] Marshall and Jolly, *loc. cit.*

The procœstrum in the bitch is characterised externally by the vulva being swollen and moistened with mucus, and by the existence, usually, but not absolutely invariably, of a flow of blood from the aperture of the vagina. The length of the procœstrum is about ten days. The sanguineous discharge generally ceases at the commencement of œstrus, which may last for another week or ten days.

Heape states that the winter œstrus in some breeds does not last so long as the summer œstrus. In certain individuals a relatively slight mucous or sanguineo-mucous flow takes place during the period of œstrus, and may even be continued beyond it, but this is exceptional. Stonehenge states that a bitch will not, as a rule, receive the dog until external bleeding has subsided, and that the most favourable time for successful coition is about the eleventh day of "heat" (in other words, at the beginning of the period of œstrus). This statement is fully borne out by dog-breeders.

The external changes which occur during "heat" are accompanied by changes in the metabolism, for Potthast,[4] working on the nitrogen metabolism of the bitch, records a slight retention of nitrogen during the "heat" period. A similar result was obtained by Hagemann,[5] who states that the retention is followed by a loss of nitrogen after copulation. Murlin[6] also shows that the effect of the procœstrum "is to cause a retention of nitrogen, which may be explained, in part at least, as a compensation for the amount of blood lost." These results should be compared with those recorded for menstruating women (see p. 63; also p. 391 and Chapter XI.).

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[1] Stonehenge, *The Dog in Health and Disease*, 4th Edition, London, 1887.

[2] Heape, *loc. cit.*

[3] Rink, *Danish Greenland*, London, 1877.

[4] Potthast, "Kenntniss des Eiweissumsatzes," *Dissertation*, Leipzig, 1887.

[5] Hagemann, "Eiweissumsatz im tierischen Organismus," *Dissertation*, Erlangen, 1891. *Cf.* also Schörndorff, "Einfluss der Schilddrüse auf den Stoffwechsel," *Pflüger's Arch.*, vol. lxvii., 1897.

[6] Murlin, "The Metabolism of Development. II. Nitrogen Balance during Pregnancy and Menstruation of the Dog," *Amer. Jour. of Physiol.*, vol. xxvii., 1910.

The histological changes which take place in the uterus during the œstrous cycle are described in the next chapter.

The period of gestation in the dog varies from fifty-nine to sixty-three days. With dogs belonging to the smaller breeds the period is often somewhat less than with large dogs. The period of lactation is very variable in duration, and may extend until the commencement of the next proœstrum. Pseudo-pregnancy may occur in the dog.

The wild dog of South America (*Canis azaræ*), according to Rengger,[1] breeds only in winter, and therefore but once a year. The same is said to be the case with the wolf[2] and the fox in their wild state; but these animals, in the Zoological Gardens in London, experience two annual "heat" periods like the dog.[3] The wolves in the Dublin Gardens, however, are stated to have only one annual sexual season when permitted to breed; otherwise they come "in heat" more frequently, but are always monœstrous.[4] The period of gestation in the wolf and fox is approximately the same as in the dog, *i.e.* about two calendar months.

Bischoff[5] refers to the fact that the sexual season of the fox is affected by the nature of the country which it inhabits, foxes which live at high altitudes breeding later than those residing on the plains. Millais[6] says that fox-cubs in most parts of Britain are not born until the end of March or beginning of April, whereas, in the South of England, they are often produced as early as January.

The Cape hunting-dog (*Lycaon pictus*) has been known to have bred in captivity on several occasions, and notably in the Gardens at Dublin, where six litters were produced from a single pair between January 1896 and January 1900. The first three litters were born in January, the fourth in November 1898, the fifth in May 1899, and the sixth in January 1900. Cunningham writes: "It is not easy to offer a satisfactory explanation of the irregularity of the fourth and fifth litters. I am inclined to believe, however, in the absence of definite information on this point obtained from the animals in a state of nature, that the lycaon breeds only once a year, and that the irregularity noticeable in the fourth and fifth litters is due to a tendency on the part of the Dublin specimens to adapt themselves to the climatic conditions of Ireland. At the same time it should be mentioned that certain indications were observed in connection with the demeanour of the parents towards each other which seemed to indicate that the sexual instinct was excited at more than one period of the year." The period of gestation was ascertained to be about eighty days, or nearly three weeks longer than in the domestic dog. "As might be expected, the young when they are born are more lusty and more advanced in development than new-born puppies of the dog." On one occasion, when the litter produced was unusually large, the gestation period was lengthened to eighty-six days.[1]

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[1] Rengger, *Naturgeschichte d. Saügethiere von Paraguay*, Basel, 1830.

[2] John Hunter (*Animal Œconomy*, London, 1786) says wolves breed in December.

[3] Heape, *loc. cit.*

[4] For the information regarding the breeding of the animals in the Royal Zoological Society's Gardens, Dublin, I am indebted to the late Professor D. J. Cunningham and Dr. R. F. Scharf. (See Marshall and Jolly, *loc. cit.*)

[5] Bischoff, "Ueber die Rauhzeit des Fuchses und die erste Entwicklung seines Eies," *Sitz. der Math.-phys.*, Wien, Classe vom 13 Juni, vol. ii., 1863.

[6] Millais, *loc. cit.*

The female of the domestic cat generally breeds two or three times a year. According to Spallanzani[2] the "heat" periods occur in February, June, and October, but there can be no doubt that many individuals breed at other times, and that there is great variation.[3] Heape[4] says that there may be no less than four sexual seasons within a year, but this can only be when the cats are not allowed to become pregnant. The usual number of litters, in my experience, is two, in typical cases in spring and autumn as in the dog. Heape states also that feral cats breed only once a year. The domestic cat is polyœstrous, and may experience a long succession of diœstrous cycles in one sexual season, each diœstrous cycle lasting about fourteen days and sometimes less.[5] The period of gestation is from fifty-six to sixty-three days.[6]

Millais[7] says it is uncertain whether the wild cat has one or two annual breeding seasons. The probability is that there is only one (in March), the young being born in May; but Millais records that he has seen young wild cats, which could not have been more than forty days old, killed in Scotland in October. Cocks, in a letter quoted by Millais, says that he has received wild cats which, judging from their size, were probably born in August or September, and that in captivity he has observed a female experience "heat" during the summer. "Many years, when owing to the death of the young, or the fact that the pair had not bred together in the spring, I have kept male and female together all summer, but they showed no inclination to breed." In a more recent letter to the author Mr. Cocks states that the old female wild cat in his possession came "in season" and received the male in the autumn of 1904, after the death of the kittens which were born earlier in the same year. The animal, however, failed to become pregnant. In the experience of this observer the commonest month for wild kittens is May, but the range of dates in his collection varies from 20th April to 22nd July. The period of gestation was ascertained to be sixty-eight days. The period of œstrus was observed to last for five days, or about the same time as in the domestic cat.

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[1] Cunningham (D. J.), "Cape Hunting Dogs (*Lycaon pictus*) in the Gardens of the Royal Zoological Society of Ireland," *Proc. Roy. Soc. Edin.*, vol. xxv., 1905.

[2] Spallanzani, *Dissertations*, vol. ii., London, 1784.

[3] Marshall and Jolly, *loc. cit.* I have known a cat experience œstrus regularly at intervals of about a fortnight from December until the following August, but such a long succession of diœstrous cycles is probably unusual.

[4] Heape, *loc. cit.*

[5] Heape, *loc. cit.* Mr. W. O. Backhouse informs me that in his experience with Siamese cats the females, if the kittens are destroyed or birth is premature, come on heat regularly about eight days after parturition. This probably occurs in other breeds, at any rate in spring and summer.

[6] There is some evidence that cats, like rabbits, may experience pseudo-pregnancy after sterile coition, since milk secretion may occur. See p. 131. (Doncaster, "A Possible Connection between Abnormal Sex-Limited Transmission and Sterility," *Proc. Camb. Phil. Soc.*, vol. xvii., 1914). Barrington shows that the glandular epithelium of Bartholin's glands in cats becomes rich in mucin shortly before œstrus and in the last half of pregnancy. ("The Variations in the Mucin Content of the Bulbo-Urethral Glands," *Internat. Monatsschr. f. Anat. und Phys.*, vol. xxx., 1913.)

[7] Millais, *loc. cit.* I am much indebted to Mr. A. H. Cocks for supplying me with interesting information concerning various Carnivora in captivity.

The male wild cat has a definite season of rut (like the stag), and calls loudly and incessantly, making far more noise than the female cat.[1] This information is interesting, since the males of most Carnivora, so far as is known, do not experience anything of the nature of a recurrent rutting season, although many individuals show indication of increased sexual activity at some times more than at others. So far as I am aware, nothing of the nature of a rutting season is ever known in the males of the domestic cat, dog, or ferret, all of which seem to be capable of coition at any period of the year. On the other hand, the males of certain seals appear to possess a season of rut at the same time as the sexual season in the females.

Little is known definitely regarding the breeding habits of the larger Felidæ in their wild state, beyond the fact that they probably agree in having a single annual sexual season. In captivity certain of them, at any rate, are polyœstrous. Thus, in the lioness œstrus has been known to recur at intervals of three weeks until the animal became pregnant, while the period of œstrus may itself last a week.[2] Further, the lioness may experience three or four sexual seasons in the year, as in the domestic cat, this having been observed to occur in the lioness in the Dublin Zoological Gardens when copulation had not been successful, or when the animals were not permitted to breed. If allowed to become pregnant the lioness at Dublin may still experience two sexual seasons, and have two litters of cubs within the year. The puma in the Dublin Gardens is stated to have one sexual season annually if breeding, or two if there is no gestation. The larger Felidæ as a rule breed comparatively freely in confinement, some places, such as the Dublin Gardens, being famous for successful lion breeding. The period of gestation in the lioness is from fifteen to sixteen weeks; that of the tigress is about twenty-two weeks; while the puma goes with young for fifteen weeks.

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[1] I am indebted to Mr. Cocks for information regarding the breeding habits of the wild cat.

[2] See Marshall and Jolly, *loc. cit.*

Most species of bears, both in their wild state and in confinement, are monœstrous and have one annual sexual season. The grizzly bear, however, according to Somerset,[1] bears young only once in two years. The bears in the Zoological Gardens at Dublin, on the other hand, may experience more than one annual sexual season if pregnancy does not occur. The period of gestation in the brown bear is seven months; in the grizzly bear it is probably longer. Heape states that with the bears in the Zoological Gardens in London œstrus may be experienced for two or three months continuously; but this condition, as he points out, is unnatural and probably an effect of confinement, for though coition can occur, it does not, as a rule, result in pregnancy.

The ferret, which is a domesticated variety of the polecat, is monœstrous, but may have as many as three annual sexual seasons,[2] which, however, instead of being distributed at regular intervals throughout the year, occur only in the spring and summer, the autumn and winter being occupied usually by a prolonged anœstrous period.[3] This tendency towards a concentration of sexual seasons during one part of the year may be considered as an approach to a condition of polyœstrum; for, if the œstrous periods were to recur at still shorter intervals than is actually the case, they could be regarded as forming so many diœstrous cycles in one sexual season. So far as I am aware, the ferret does not experience œstrus more than twice annually if allowed to breed.

The polecat is also monœstrous, but breeds only once a year. Mr. Cocks informs me that in captivity the young of this animal are generally born in the first half of June, and that the gestation period, as in the ferret, is about forty days.

The stoat, weasel, and pine-marten, in their wild state, are almost certainly monœstrous and breed once a year. In the last-mentioned animal Cocks[1] found that a single œstrus may last a fortnight. The stoat and weasel do not appear to have been bred in captivity. The otter in a state of nature breeds only once a twelvemonth (in winter, as a rule, but young may be born at any season according to Cocks). In captivity, however, œstrus may recur at regular monthly intervals all the year round.[2]

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[1] Somerset. Quoted by Heape, *loc. cit.*

[2] Carnegie, *Ferrets and Ferreting*, London.

[3] Robinson ("The Formation, Rupture, and Closure of Ovarian Follicles in Ferrets, etc.," *Trans. Roy. Soc. Edin.*, vol. lii., 1918) finds that the size of the ovary varies at different periods. It is smallest in the anœstrum and largest about mid-pregnancy. At œstrus it is intermediate.

The various species of seals are in all probability monœstrous, and have one litter of young annually. Some species show an almost perfect rhythmic regularity in the recurrence of their breeding season. Thus, in the case of the harp seal in the north-east of Newfoundland, and also in Greenland, according to Millais,[3] the pups are born each year between 8th and 10th March. Farther north, however, at Jan Mayen, they are not born until about 23rd or 24th March. Turner's notes[4] on the breeding habits of seals also point to the conclusion that the sexual season with these animals is restricted to regular periods of comparatively short duration, so that it may probably be assumed that seals are monœstrous. The males of seals, as already remarked, experience rut at the time of the female sexual season. Whether the male generative organs are functional (*e.g.* whether the testes produce sperms) at other times does not appear to be known. It is of interest to note that in many species the rut is experienced during a period of complete fasting. Thus it is stated that the male fur seal, after coming to land, may live for over a hundred days without taking food, and that during this period he is constantly engaged in struggles with other males, finally leaving the shore in a state of extreme emaciation.

The walrus affords an example of a mammal which bears young only once in three years. Parturition takes place about May or June, and the sexual season recurs about two years subsequently.

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[1] Cocks, "Note on the Gestation of the Pine-Marten," *Proc. Zool. Soc.*, 1900.

[2] Cocks, "Note on the Breeding of the Otter," *Proc. Zool. Soc.*, 1881. Mr. Cocks' subsequent experience, concerning which he has been kind enough to write to me, confirms the conclusion that there is no anœstrous period in the otter in captivity. There has been some controversy regarding the breeding of the badger. According to Meade-Waldo the period of gestation is between four and five months ("The Badger: its Period of Gestation," *Zoologist*, 1894), but according to Cocks ("The Gestation of the Badger," *Zoologist*, 1903, 1904), this period may be anything between under five and over fifteen months, for although the sexual season may apparently occur at any time of the year, the young are invariably born within a period limited to six weeks. This extraordinary conclusion is based on a number of observations. Fries ("Über die Fortpflanzung von *Meles taxus*," *Zool. Anz.*, vol. iii., 1880) describes the badger's ovum as undergoing a resting state during which development is at a standstill (*cf.* roe-deer, p. 43).

[3] Millais, *loc. cit.*

[4] Turner, "On the Placentation of Seals," *Trans. Roy. Soc. Edin.*, vol. xxvii., 1875.

Thus the nursing or lactation period extends for nearly two years, while gestation lasts about one year.[1]

INSECTIVORA

The majority of the animals in this order are almost certainly polyœstrous, but comparatively little is known concerning their breeding habits. The shrew in this country may be found breeding in any month from April until November, so that it is practically certain that this animal is polyœstrous, and may have two litters, if not three litters, in a year. It is extremely probable also that the water-shrew breeds twice a year. In the hedgehog, in this country, litters are born at the end of May or June, and in August or September.[2] In Germany it is said that the breeding season extends from March until July.[3] The period of gestation in the hedgehog is not more than one month. The Malayan hedgehogs *Gymnura* and *Hylomys* are stated to experience an uninterrupted polyœstrum.

In the mole a great development of the male generative organs begins to take place at the end of January, culminating at the end of March. Previous to the end of January it is a matter of great difficulty to distinguish the males from the females without having recourse to dissection. The testicles lie on each side of the urinary bladder within the peritoneal cavity. In March they are protruded into sacs, which look like a continuation of the peritoneal cavity beneath the base of the tail. According to Regaud and Lécaillon they increase in size sixty-four times.[4] Meanwhile the seminiferous tubules within the testicles undergo enlargement, and cells are proliferated, which give origin to the spermatozoa. The prostatic glands, which begin to increase in size in February, acquire enormous dimensions, and conceal the urinary bladder at the end of March[5] (*cf.* hedgehog, p. 250). At the beginning of the breeding season the male moles fight one another with great ferocity, and one is often killed. Pairing takes place at the end of March, or in April, or sometimes as late as early May. A second litter of moles may be born later in the year, but this fact has not been definitely proved.[1]

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[1] Millais, *loc. cit.*

[2] Millais, *The Mammals of Great Britain and Ireland*, vol. i., London, 1904.

[3] Van Herwerden, "Beitrag zur Kenntniss des menstruellen Cyklus," *Monatsschr. f. Geburtshülfe und Gynäk.*, vol. xxiv., 1906. For further information see Marshall, "The Male Generative Cycle in the Hedgehog," *Jour. of Physiol.*, vol. xliii., 1911; and Tandler and Gross, *Arch. f. Entwick. Mech.*, vol. xxxiii., 1911.

[4] Adams, "Sexual Life of Mole," *Jour. Ministry of Agric.*, vol. xxxvii., 1920. Regaud, "État des Cellules Interstialles chez la Taupe," *C.R. de l'Assoc. Anat.*, Suppl., 1904. Lécaillon, "Sur les Cellules Interstialles du Testicule de la Taupe," *C.R. de la Soc. de Biol.*, vol. lxvi., 1909.

[5] Owen, *loc. cit.* The same authority states that in the Cape mole (*Chrysochloris*) he found the testes near the kidneys, but that the vasa deferentia had a convoluted course, which showed that they underwent periodic movements. Owen also describes the vesiculæ seminales in the hedgehog as growing to an enormous size at the season of rut.

It would appear that in some Insectivores the proœstrum may be comparatively severe, for in *Tupaia javanica* Stratz[2] has described a "menstrual" blood-clot which contained pieces of desquamated epithelium.

CHEIROPTERA

As will be explained more fully in a future chapter, some species of bats appear to be exceptional in that the season of œstrus does not synchronise with the period of ovulation. It has been shown by Benecke,[3] Eimer,[4] van Beneden,[5] and Salvi, that whereas copulation may occur in the autumn, the ova are not fertilised until after the winter hibernation, the spermatozoa in the meantime lying dormant. Salvi,[6] however, describes the bats in the Grotta dell' Inferno, near Sassari, as copulating also in the spring, but it is suggested that coition at this season may only take place among those females which have failed to become inseminated effectively in the previous autumn.[7] It does not appear to be known whether the polyœstrous condition ever occurs in bats.

It is stated that a "menstrual" (proœstrous) flow has been observed in the flying fox (*Pteropus*).[8]

PRIMATES

Lemurs.—Among Lemuroids, Stratz[9] has shown that in *Tarsius spectrum* there is a sanguineous proœstrous discharge almost as concentrated as in monkeys. This is presumably followed by an œstrous period. It is stated also that *Tarsius* experiences an uninterrupted series of diœstrous cycles (*i.e.* a condition of continuous polyœstrum); but that, whereas conception is possible at any time of the year, breeding occurs more frequently in October and November than at other seasons.[10]

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[1] Millais, *loc. cit.* See also Adams, "A Contribution to our Knowledge of the Mole," *Manchester Lit. and Phil. Soc. Mem.*, 1902.

[2] Stratz, *Der geschlechtsreife Saügethiereierstock*, Haag, 1898.

[3] Benecke, "Ueber Reifung und Befruchtung des Eies bei den Fledermäusen," *Zool. Anz.*, vol. ii., 1879.

[4] Eimer, "Ueber die Fortpflanzung der Fledermäuse," *Zool. Anz.*, vol. ii., 1879.

[5] Van Beneden, "Observations sur la Maturation, la Fécondation, et la Segmentation de l'œuf chez les Cheiroptères," *Arch. de Biol.*, vol. i., 1880.

[6] Salvi, "Osservazioni sopra l'Accoppiamento dei Chirotteri nostrani," *Atti della Società Toscana di Scienze Naturali*, vol. xii., 1901.

[7] Duval, *Etudes sur l'Embryologie des Cheiroptères*, Première Partie, Paris, 1899.

[8] Wiltshire, *loc. cit.*

[9] Stratz, *loc. cit.*

[10] Van Herwerden, *loc. cit.*

Monkeys.—The essential similarity between the procœstrum in the lower Mammalia and menstruation in monkeys will be made clear in the next chapter, when the histological changes which occur in the uterus are described. The consideration of the subject, however, is somewhat complicated by the fact pointed out by Heape[1] that, whereas monkeys may have a continuous series of diœstrous cycles usually at regular monthly intervals, they are not necessarily capable of breeding at every heat period. Thus there is evidence that in the gorilla and chimpanzee in West Africa and in the orang-utan of Borneo and the Eastern Archipelago there are special sexual seasons,[2] and Heape[3] has shown that the same can be said of *Semnopithecus entellus* and *Macacus rhesus* in India, but that the exact time for breeding varies in the different localities. Thus in Simla *Macacus rhesus* copulates about October, and gives birth to young about August or September in the following year, whereas on the plains around Muttra it seems probable that March is the usual month when young are born. Hingston[4] states that in the Himalayas the Rhesus monkeys pair in September and the young are born in March. However, Mr. Sányál, the Superintendent of the Zoological Gardens in Calcutta, expressed the opinion that *M. rhesus* can breed at all times of the year.[3] On the other hand, it has been shown by van Herwerden[5] that *Cercocebus* in the island of Banha breeds only, as a rule, in the late summer or early autumn.

Heape[6] states that with the *Macacus* in the Gardens in London there is definite œstrus which always occurs after the cessation of the menstrual discharge, and persists for two or three days, and Ellis[7] has shown that this is also probably the case with the orang-utan as well as with various monkeys.

Pocock[8] has given some interesting details concerning the phenomena which attend the menstrual process in various monkeys and baboons in the Zoological Society's Gardens. He states that the females of many species at about the time of menstruation exhibit extreme congestion of the naked area surrounding the genital and anal orifices. Such a swelling was noticed in various species of *Cercocebus* and *Papio*, and in *Macacus nemestrinus*,[1] but not in *Cercopithecus*, or in certain other species of *Macacus* including *M. rhesus*. Heape, however, states that in menstruating specimens of *M. rhesus* observed by him, and *M. cynomolgus*, the skin of the buttocks became swollen and red or purple in colour, as well as the skin of the abdomen, the inside of the thighs, and the under surface of the tail, while the skin of the face tended to become flushed or blotched with red; at the same time the nipples and vulva were congested. Menstrual hæmorrhage has been recorded in many monkeys and baboons, but there appears to be considerable variability in its extent. Pocock says: "In baboons it may or may not take place, and may be great or little in amount. It has been noticed to occur in some profusion in a female of *Macacus sinicus*, and not to occur appreciably in a female of the closely allied species, *M. fascicularis*. Obviously, therefore, it cannot be associated with the inflammatory swelling of the genito-anal region [since no swelling was apparent in either of these two species]; and it is hardly likely to have a specific value in taxonomy. Perhaps the nearest guess that can at present be made is the surmise that it is dependent on the constitution or health of the individual."

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[1] Heape, *loc. cit.*

[2] Winwood Reade, *Savage Africa*, London. Mohrike, *Das Ausland*, 1872. Garner, *Gorillas and Chimpanzees*, 1896. Burton (*Trips to Gorilla Land*, vol. i., London, 1876) says that the gorilla breeds about December, a cool, dry month, and that the period of gestation is five to six months.

[3] Heape, "The Menstruation of *Semnopithecus entellus*," *Phil. Trans.*, B., vol. clxxxv., 1894, "The Menstruation and Ovulation of *Macacus rhesus*," *Phil. Trans.*, B., vol. clxxxviii., 1897.

[4] Hingston, *A Naturalist in Himalaya*, London, 1920.

[5] Van Herwerden, *loc. cit.*

[6] Heape, *The Sexual Season*, etc.

[7] Havelock Ellis, *Psychology of Sex*, vol. ii., Philadelphia, 1900.

[8] Pocock, "Notes upon Menstruation, Gestation, and Parturition of some Monkeys that have lived in the Society's Gardens," *Proc. Zool. Soc.*, 1906.

Heape noticed that in *M. rhesus* the menstrual discharge lasted for from three to five days. Pocock records that in a Chacma baboon (*Papio porcarius*) hæmorrhage continued for about four days. In both animals the phenomenon was truly "menstrual" (*i.e.* of monthly occurrence).

Pocock records the interesting fact that whereas the swelling of the congested area commences at about the same time as the hæmorrhage, it does not reach its full size until several days after the discharge is over. It soon afterwards begins to shrink, and in about another two weeks has disappeared, so that the female at a distance is indistinguishable from the male. After a few days' rest congestion again sets in, and the process is repeated. Pocock suggests that this sub-caudal swelling may serve the purpose of apprising the male (at a distance) as to when the female is "on heat," and it is to be noted that it is at its maximum after menstruation is over (as just mentioned), and so presumably therefore during a definite period of œstrus.

The question as to the correspondence in time between the processes of menstruation and ovulation is discussed in a later chapter.

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[1] Similar observations had been previously described in *Cercopithecus*, *Papio*, and other species by certain of the older naturalists. See St. Hilaire and Cuvier, *Hist. Nat. des Mammifères*, 1819-35.

Little is definitely known concerning the length of the gestation period in the various apes and monkeys. Pocock's observations show that in *Macacus nemestrinus* this period is between six and seven months. Blandford[1] states his belief that about seven months is the usual period for the genus *Macacus*. Sányál, according to information recorded by Sclater,[2] found that a female of *Cercopithecus cynosurus* in the Zoological Gardens, Calcutta, carried her young for seven months.

Gestation in the Quadrumana is dealt with at some length by Breschet,[3] who cites many of the older observations. He shows that the question as to the duration of the period is complicated by the fact that monkeys, unlike the majority of Mammals, may copulate at other times than the breeding season, and that they are said occasionally to experience menstruation during pregnancy.

Man.—As is well known, menstruation recurs normally in the non-pregnant human female at intervals of from twenty-eight to thirty days. The exceptions to this general rule are, however, very numerous, and have often been noticed. Thus the interval may be extended to five weeks, or be abbreviated to two weeks without any derangement to the general health. "In one hundred women, sixty-one [were found] to menstruate every month, twenty-eight every three weeks, ten at uncertain intervals, and one, a healthy woman aged twenty-three years, every fortnight."[4] The duration and amount of the discharge may also vary considerably both in different women and in the same woman at different times.

It has been supposed by many from classical times onwards, that menstruation is directly associated with lunar periodicity. Thus Aristotle[5] says that it occurs during the waning of the moon. In recent times Arrhenius,[6] as a result of a statistical examination of 12,000 cases, found a periodicity corresponding to the tropical lunar month of 27·32 days (and not to the synodic period of 29·53 days, and hence with the moon's phases); that is to say, that although women menstruate at all times, yet more do so at a certain part of the tropical lunar period than at other parts. The inference drawn is that the moon's declination may have been one factor among a number that determine the time of menstruation. Such a conclusion, however, must be accepted with great reservation seeing that the diœstrous cycle in the lower Mammals may be three weeks or fifteen days, or some other period having no relation to lunar periodicity.

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[1] Blandford, *The Fauna of British India*, vol. i., London, 1888.

[2] Sclater, *Mammals of South Africa*, London.

[3] Breschet, "Recherches anatomiques et physiologiques sur la Gestation des Quadrumanes," *Mémoires de l'Acad. des Sciences*, vol. xix., 1845.

[4] Laycock, *loc. cit.*, and Havelock Ellis, *loc. cit.* There is in some cases a tendency for the cycle to become divided up into two cycles, separated by the so-called "Mittelschmerz," or inter-menstrual pain, which is occasionally accompanied by a sanguineous discharge. (Halliday Croom, "Mittelschmerz," *Trans. Edin. Obstet. Soc.*, vol. xxi., 1896.)

[5] Aristotle, *Historia Animalium* (*The Works of Aristotle*, vol. iv., Thompson's Translation, Oxford, 1910) and *De Generatione Animalium* (vol. v., Platt's Translation, Oxford, 1912).

[6] Arrhenius, "Die Einwirkung kosmischer Einflusse an physiologischen Verhältnisse," *Skandin. Arch. f. Physiol.*, vol. viii., 1898.

It is stated, also, that the periodicity of menstruation depends partly on the climatic conditions, and that women in Lapland and Greenland menstruate less frequently, whereas in certain low and hot countries the catamenia may recur every three weeks.[1]

Further, the regularity with which the menstrual periods occur is liable to be disturbed by environmental changes. Thus, it is stated that change of residence, or foreign travel, without otherwise affecting the health, may bring about amenorrhœa or a temporary cessation of menstruation.[2] Such an effect is, no doubt, comparable to the well-known influence of captivity or change of environment in arresting the sexual functions of many animals.

The commonest time for the continuance of the menstrual flow is said to be about three or four days in this country, but it may last for as long as eight days, or, on the other hand, for only a few hours without disturbance of health. It usually begins gradually, becoming most profuse about the second or third day, and then diminishes.[3] The total amount of blood lost has been variously estimated at from two to four ounces. In hot climates the quantity is greater than in cold; and it is said to be increased by luxurious living, and also by abnormal mental stimulation. The character of the menstrual discharge and its source of origin can best be considered in describing the histology of the uterus during the œstrous and menstrual cycles (see Chapter III.).

The monthly development of the uterine mucous membrane which precedes the menstrual discharge is often accompanied by a fullness of the breasts which begins to disappear after the commencement of the flow. Swelling of the thyroid and parotid glands, and tonsils, as well as congestion of the skin and a tendency towards the formation of pigment, are also known to occur.[1] The voice also is liable to be affected at the menstrual periods, and the skin and breath sometimes have a peculiar odour. Mental depression may exist, and be accompanied by nervous pathological phenomena.

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[1] Matthews Duncan, "Sterility in Women," *Brit. Med. Jour.*, 1883; and Laycock, *loc. cit.*

[2] Wiltshire, *loc. cit.*

[3] Galabin, *A Manual of Midwifery*, 6th Edition, London, 1904. The age at which menstruation begins varies in different countries, being earlier in warm climates than in cold ones. In our own country the first menstruation does not usually occur before the age of fourteen or fifteen, while the menopause (or period when menstruation ceases) begins about the age of forty-five. (See p. 715.) Kennedy (*Edin. Med. Jour.*, vol. xxvii., 1882), however, has reported a case of a woman who continued to menstruate after giving birth to a child at the age of sixty-three.

Many women are more excitable before the onset of menstruation and others during the process. With the onset the pulse-rate, blood pressure, and temperature generally rise. The bacterial resistance of the subject is reduced. After menstruation there is a period of slackness, sometimes associated with headache and depression.

As Head has pointed out, the general bodily state at the menstrual periods forms a potent cause of diminished automatic control by the central nervous system. "This physiological act may be accompanied by referred pain, confined strictly to those segments which stand in direct relation with the pelvic organs, or the morbid sensations may occupy the whole of the body and lower extremities below the level of the umbilicus, with or without the cervical areas and occipital region of the scalp. Finally, the head, trunk, and even the limbs may become painful and tender in parts that have no direct relation to stimuli within the pelvic organs. The extent to which such widespread generalisation occurs, depends more on the temperamental condition of the patient than on the intensity of the painful irritation."[2] This diffusion of painful sensation is due to diminished central resistance; potentially painful impulses which would normally have been inhibited or strictly confined to areas appropriate to the organ affected are allowed to spread widely. There is a tendency during menstruation to react more vividly to any excitation capable of evoking discomfort.

Painful menstruation, when so pronounced as to be considered pathological, is called dysmenorrhœa; diffuse or protracted menstruation is termed menorrhagia; but there are all gradations between these conditions and normality.[3]

According to the upholders of the "Wellenbewegung" hypothesis[4] the reproductive life of the human female consists of a succession of wave-like periods which follow the monthly cycle. Thus, according to Stevenson,[5] the curve of temperature is above the mean line for about half the month, when it rises to half a degree above the mean. It falls below the mean line just before the onset of menstruation, during which it remains about half a degree below. Similar results were obtained by Reinl, Ott, and Giles,[1] but Vicarelli[2] and certain other authors have recorded an increased temperature during menstruation.[3] Zuntz,[4] however, as a result of more recent experiments, says that there is a regular lowering of the temperature throughout the menstrual period, after which it rises to the normal.

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[1] See p. 384, Chapter IX.

[2] Head, "The Release of Function in the Nervous System," Croonian Lecture, *Proc. Roy. Soc.*, B., vol. xcii., 1921.

[3] For amenorrhœa, see pp. 60 and 69.

[4] Godman, "The Cyclical Theory of Menstruation," *Amer. Jour. Obstet.*, vol. xi., 1878. Reinl, "Die Wellenbewegung des Lebensprozesses des Weibes," *Volkmann's Sammlung klin. Vorträge*, No. 273. Ott, "Les lois de la périodicité de la fonction physiologique dans l'organisme féminine," *Nouvelles Arch. d'Obstet. et de Gynéc.*, 1890. See also Havelock Ellis, *Man and Woman: a Study of Human Secondary Sexual Characters*, 5th Edition, London, 1914. This work contains a fund of valuable information.

[5] Stevenson, "On the Menstrual Wave," *Amer. Jour. Obstet.*, vol. xv., 1882.

Stevenson states also that the curve of urea excretion follows a similar course to the temperature curve, and that, speaking generally, there is an increase in metabolism coincident with the time of development of the uterine mucosa. There is, however, no doubt much truth in von Noorden's criticism[5] that the "menstrual wave" hypothesis has given occasion to many premature conclusions

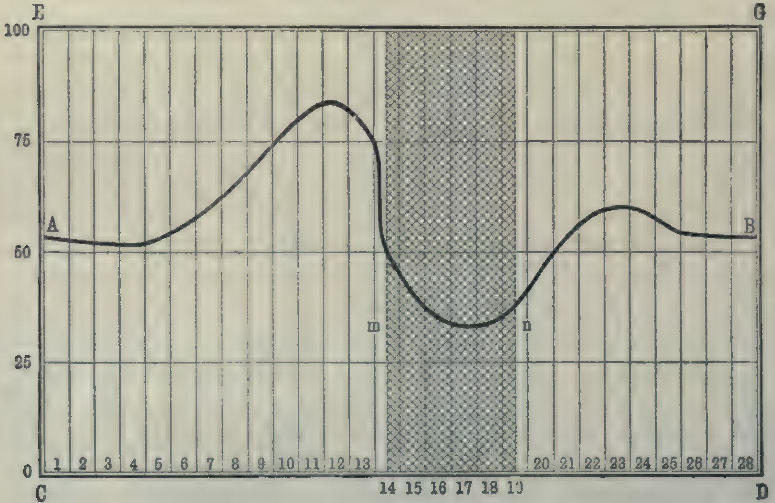

FIG. 1.—Diagram illustrating the "Wellenbewegung" hypothesis. The curve AB represents the varying intensity of the vital processes during the twenty-eight days of the menstrual cycle. The numbers between *m* and *n* represent the days occupied by menstruation. (From Sellheim.)

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[1] Giles, "The Cyclical or Wave Theory, etc.," *Trans. Obstet. Soc.*, London, vol. xxxix., 1897.

[2] Vicarelli, "La température de l'utérus dans ses diverses conditions physiologiques," *Arch. Ital. de Biol.*, vol. xxxii., 1899.

[3] Sfameni, "Influence de la menstruation sur la quantité d'hémoglobine," *Arch. Ital. de Biol.*, vol. xxxii., 1899.

[4] Zuntz (L.), "Einfluss der Ovarien auf den Stoffwechsel," *Arch. f. Gynäk.*, vol. lxxviii., 1906.

[5] Von Noorden, *Metabolism and Practical Medicine* (English Translation), vol. i., London, 1907.

regarding the behaviour of the metabolism. Schroder,[1] who investigated the nitrogen metabolism, found a retention of nitrogen immediately before and during menstruation (*cf.* Potthast, etc., for dogs, p. 49), but other investigators have obtained somewhat different results.[2] Zuntz has shown from numerous experiments that, contrary to the conclusions of other authors, there is no evidence of a constant variation in the respiratory exchange during the menstrual cycle. (For changes during pregnancy, see Chapter XI.)

Mosher[3] states that there is a fall of blood pressure at the time of menstruation. Zuntz[4] records a diminution in the pulse-rate.

Sfameni[5] states that there is a decrease in the quantity of hæmoglobin in the blood during menstruation. He says also that the number of blood corpuscles increases in the days immediately preceding the hæmorrhage, but is diminished during it.[6]

Birnbaum and Osten[7] state that in the blood of menstruating women coagulation is retarded. This statement is based on experiments made by adding fibrinogen to menstrual blood-serum.

Blair Bell[8] states that in connection with menstruation there is a marked drop in the calcium content of the systemic blood, and that this is most marked just before bleeding begins. This is correlated with an excretion of calcium salts in the menstrual discharge, an examination of which revealed the presence of a considerable quantity of calcium, both free and within the leucocytes (see p. 81). This excretion of calcium during menstruation is regarded by Blair Bell as connected phylogenetically with the process of egg-formation by birds and other lower Vertebrates.

Further, this author is disposed to believe that the calcium metabolism, under the direction of the ovaries and other ductless glands, is concerned in the phenomena of menstruation. He refers especially to the following points: (1) Calcium salts are necessary for the repair of all lesions. Therefore the presence of menstruation is dependent upon a healthy condition of the organism, and its claims on the calcium metabolism at any particular time (*cf.* absence of menstruation during lactation when calcium salts in quantity are required for the milk). (2) Uterine contractions are, like other involuntary muscle contractions, largely dependent upon the calcium salts circulating in the blood. (3) Calcium salts have a powerful effect on the vasomotor system, which is greatly affected during menstruation and the menopause. (4) Menstruation does not begin until puberty, when the bony framework has been laid down.[1]

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[1] Schroder, "Untersuchungen über den Stoffwechsel während der Menstruation," *Zeitschr. f. klin. Medicin*, vol. xxv., 1894.

[2] See von Noorden, *loc. cit.*

[3] Mosher, "Blood-pressure during Menstruation," *Johns Hopkins Hospital Bulletin*, 1901.

[4] Zuntz, *loc. cit.*

[5] Sfameni, *loc. cit.*

[6] *Cf.* Carnot and Deflandre, "Variations du nombre des Hématies chez la Femme pendant la période menstruelle," *C. R. de la Soc. de Biol.*, vol. lxvi., 1909.

[7] Birnbaum and Osten, "Untersuchungen über die Gerinnung des Blutes während der Menstruation," *Arch. f. Gynäk.*, vol. lxxx., 1906.

[8] Blair Bell, "Menstruation and its Relation to the Calcium Metabolism," *Proc. Roy. Soc. Med.*, July 1908. See also below, p. 389.

According to Hare[2] menstruation is the result of a progressive accumulation of carbonaceous material in the blood. In animals excessive muscular activity is a substitute. On this view, for which Hare presents general evidence, menstruation is a means of getting rid of an anabolic surplus.

According to Martin,[3] and certain other writers, the human female often experiences a distinct post-menstrual œstrus, at which sexual desire is greater than at other times; so that, although conception can occur throughout the inter-menstrual periods, it would seem probable that originally coition was restricted to definite periods of œstrus following menstrual or proœstrous periods in women as in the females of other Mammalia. On this point Heape writes as follows: "This special time for œstrus in the human female has very frequently been denied, and, no doubt, modern civilisation and modern social life do much to check the natural sexual instinct where there is undue strain on the constitution, or to stimulate it at other times where extreme vigour is the result. For these reasons a definite period of œstrus may readily be interfered with, but the instinct is, I am convinced, still marked."[4]

Mall,[5] as a result of the study of thirty-six cases, has come to the conclusion that fertile coition is most likely to occur between the fourth and thirteenth days after the first day of the appearance of the menstrual discharge. This is further evidence of a post-menstrual œstrus. Mall supposes that there is on an average a one-day interval between coition and the fertilisation of the ovum.

Heape has also given a brief résumé of the evidence that primitive man resembled the lower Primates in having a definite sexual season. The evidence is based largely upon the works of Ploss[1] and Westermarck,[2] the latter of whom goes somewhat fully into the subject in a chapter on "A Human Pairing Season in Primitive Times," to which the reader is referred for further references on this subject.[3]

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[1] Blair Bell, *The Principles of Gynæcology*, London, 1910.

[2] Hare, "The Meaning and Mechanism of Menstruation," *Clinical Journal*, 1916.

[3] Martin, "The Physiology and Histology of Ovulation, Menstruation, and Fertilisation" Hirst's *System of Obstetrics*, vol. i., London, 1888.

[4] Heape, *loc. cit.* According to Stopes (*Married Love*, London, 1918) there may be two periods of increased sexual desire in the human subject during one menstrual cycle, but it is not suggested that the second period is in any way correlated with the "Mittelschmerz." If Stopes is correct it is difficult to compare the menstrual cycle of man with the œstrous cycle of the lower Mammals.

[5] Mall, "On the Age of Human Embryos," *Amer. Jour. of Anat.*, vol. xxiii., 1918.

It has been shown that there is a more or less restricted season for breeding among certain of the North American Indians, among certain tribes in Hindustan, among many of the native Australians, among the Esquimaux, among the natives of the Andaman Islands, as well as among certain other of the more primitive races of mankind. The season seems generally to occur in the spring, but this is not invariably so. Annandale and Robinson[4] state that among the Semang or aboriginal tribes of the Siamese State of Jalor, children are generally born only in March, or immediately after the wet season, a fact which appears to imply that there is a regular sexual season in June.

Further evidence of the existence of a primitive sexual season in man is furnished by the records of the annual feasts which the ancients indulged in—usually in the spring—and which Frazer[5] has shown to be represented in modern European countries by the May-queen festivals, and other similar customs that have survived into our own time. It is well known that the ancient festivals among the civilised peoples of the past were times of great sexual licence, and so in all probability were similar in origin to the licentious feasts and dances of various savage races at the present day. Their anthropological significance and the intimate association between them and the idea of reproduction are discussed at great length by Frazer in his book entitled "The Golden Bough."

There is, moreover, evidence of a human pairing season in the higher birth-rate which occurs at certain seasons in various countries at the present day. Ploss has collected statistics illustrating this fact in Russia, France, Italy, and Germany, and Haycraft[6] has shown that there are indications of a similar condition existing in Scotland. On this subject Mayo-Smith[7] writes as follows: "The largest number [of births] almost always falls in the month of February . . . corresponding to conceptions in May and June. . . . Observations tend to show the largest number of conceptions in Sweden falling in June; in Holland and France, in May-June; in Spain, Austria, and Italy, in May; in Greece, in April. That is, the farther south, the earlier the spring and the earlier the conceptions." Other facts of a like kind are recorded by Westermarck, who concludes that primitive man had an innate tendency towards increased powers of reproduction at the end of spring or beginning of summer, and that this tendency became variously modified under the influence of natural selection in the different human races which subsequently arose.[1]

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[1] Ploss, *Das Weib*, Leipzig, 1895.

[2] Westermarck, *The History of Human Marriage*, London, 1891; 5th Edition, 1921.

[3] See also Havelock Ellis, *loc. cit.*

[4] Annandale and Robinson, *Fasciculi Malayenses: Anthropology*, Part I., 1903.

[5] Frazer, *The Golden Bough*, 2nd Edition, London, 1900; 3rd Edition, in thirteen volumes, published at intervals subsequently.

[6] Haycraft, "On some Physiological Results of Temperature Variations," *Trans. Roy. Soc. Edin.*, vol. xxix., 1880.

[7] Mayo-Smith, *Statistics and Sociology*, vol. i., New York, 1895. *Cf.* also van Herwerden, *loc. cit.*

Finally, it may be pointed out that Westermarck's conclusion—which seems a very probable one in view of the evidence which he and others have collected—is in no way invalidated by the fact that the human female experiences normally an uninterrupted succession of diœstrous (*i.e.* menstrual) cycles; for, as already shown, a similar condition is known to exist in several at least of the lower Primates, with which there is also evidence that in a state of nature the breeding functions are restricted to particular seasons of the year.[2]

Whether the monœstrous or the polyœstrous condition is the more primitive is a question which cannot at present be decided. The fact that polyœstrum is secondarily acquired among many animals may perhaps be regarded as evidence that monœstrum is the more primitive of the two conditions; for, as already shown, there are numerous instances of Mammals which are almost certainly monœstrous in their wild state, but which have independently assumed a condition of polyœstrum under the more luxurious influences of domestication. Thus, while the sheep, the sow, and the cat are almost certainly monœstrous in a state of nature, the domesticated breeds of these animals show a varying degree of polyœstrum which appears to depend largely upon the extent to which domestication has been carried as well as upon food and the influences of the surroundings. On the other hand, the existence of the continuous polyœstrum in tropical climates among such primitive Mammals as the Insectivores, and the common occurrence of varying degrees of polyœstrum among the Rodents, not only in captivity but also in the wild state, point to the possibility that polyœstrum may be the more primitive condition, and one which can easily be reverted to under the influence of a favourable environment.

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[1] Mayo-Smith (*loc. cit.*) points out that sexual periodicity in civilised man is much obscured by social influences. "One great social influence is the time of marriage. Marriage tends to accumulate about the social festivities of Christmas time, and in Catholic countries especially in the period just before Lent." He suggests that in agricultural districts the concentration about Christmas is due to the leisure following the labours of the autumn. "In cities the births are more evenly distributed, showing that artificial life has overcome the influence of seasons and particular occupations."

[2] That is to say that, whereas menstruation goes on at regular intervals all the year round, the proœstrous or menstrual periods are only followed during the breeding season by œstri at which it is possible for conception to occur. There are some indications that the sexual instinct among males is also periodic, both in the lower Primates and in the human subject, but the periodicity is not so marked as among females. Havelock Ellis (*loc. cit.*) has discussed this question at some length, adducing evidence of a sexual rhythm in men. See especially appendix to Ellis's work by Perry-Coste, who shows that there may be a tendency towards rhythmic regularity in the sexual functions as manifested especially in the recurrence of seminal emissions.

Hill and O'Donoghue[1] are of opinion that the monœstrous condition is the more primitive, basing their conclusion on what is known of the breeding habits of the Marsupials, *e.g. Dasyurus, Trichosurus, Phascolarctus*, and *Phascolomys*, and Monotremes, which are the most primitive of all Mammals, as well as on considerations relative to the sexual functions in reptiles, and this conclusion we may tentatively accept as correct. It has already been mentioned that in monœstrous animals like *Dasyurus* and the dog œstrus, if not succeeded by pregnancy, is followed by pseudo-pregnancy, and both these conditions are associated with the persistence of the corpus luteum or glandular structure formed from the discharged follicle after the expulsion of the ovum. In acquiring the polyœstrous habit the duration of the corpus luteum has been much shortened down, and the period of pseudo-pregnancy has almost or quite disappeared so as to make way for a new ovulation and the associated changes of œstrus.

The main purpose of polyœstrum (to use teleological language) is no doubt, as already remarked, to provide increased opportunity for coition, and so to promote the fecundity of the race. But it must be remembered that œstrus is not necessarily associated with ovulation, and consequently the explanation just given of the polyœstrous habit is not of universal application. This is a point which will be referred to again in dealing with ovulation. It is of course possible, however, that the polyœstrous condition, having once been acquired, might in certain circumstances be perpetuated in spite of its inutility.

Before concluding the present chapter it remains for me to allude briefly to the effect of maternal influences on the œstrous cycle. These, as pointed out by Heape, may or may not completely disorganise the recurrence of the sexual season. In such animals as the dog they do not do so, because the dog is monœstrous, and has, as a rule, only two sexual seasons annually, so that the anœstrous period considerably exceeds in length the period of gestation. In large animals such as the camel, on the other hand, where the gestation period extends for thirteen months, the recurrence of the sexual season is postponed by pregnancy for a whole year. Again, in small animals like the rat, gestation only prevents the recurrence of œstrus, reducing the number of diœstrous cycles, but not interfering with the recurrence of the sexual season. "But whenever gestation occurs it encroaches upon, if it does not entirely absorb, the anœstrum; that is to say, it reduces the period during which the generative organs would lie fallow if the sexual season were a barren one. Thus in the case of a mare, a barren sexual season may consist of a series of diœstrous cycles lasting for as long as six months, in which case the anœstrum lasts six months also, after which another sexual season begins. A reproductive sexual season, however, results in a period of eleven months' gestation, interfering not only with the diœstrous cycles which would have recurred if conception had not taken place, but also absorbing practically the whole of the anœstrum."[1]

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[1] Hill and O'Donoghue, *loc. cit.*

The duration of the gestation period is intimately connected not only with the size of the body,[2] but also with the stage of development at which the young are born.[3] It is longest in the large terrestrial and gigantic aquatic Mammals (Ungulata and Cetacea), which live amid favourable conditions of nourishment. With these animals the young are so far advanced in development at the time of birth that they are able to follow the mother about, and to a certain extent shift for themselves. In Carnivores and Rodents the period of pregnancy is relatively shorter, and the young are often born naked, and with unopened eyes, and consequently are absolutely helpless for a considerable time after birth. The gestation period is shortest in the aplacental Mammals (Monotremata and Marsupialia), in which the young are born at a very early stage and transferred to a pouch formed by cutaneous folds in the vaginal region. In Monotremes the young are hatched from eggs which, after being laid, are deposited in the pouch.

The question as to what are the precise factors which determine the length of the gestation period has already been referred to in the first chapter, where it was pointed out that both the duration of pregnancy and the time of the year at which breeding occurs are necessarily controlled by natural selection, acting in the interests of the next generation.

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[1] Heape, *loc. cit.*

[2] The period of gestation is 144 days in Southdown sheep and 150 in Merinos which are larger, while the hybrid is intermediate. (Lydekker, *The Sheep and its Cousins*, London, 1912.) The causes which determine the variation in the gestation period within any one species have been investigated by Dussogno, who found that in pigs neither the size, weight, nor predominant sex of the litter affected the gestation period, but that it appeared to vary with the age, vigour, and condition of the sow. ("Sulla durata della gravidanza nelle Scrofe Yorkshires," *L'Industria latticea e Zootecnica*, 1915.)

[3] Sedgwick, *Student's Text-Book of Zoology*, vol. ii., London, 1905.

The effects of lactation upon the recurrence of œstrus vary widely, and are often different among individuals belonging to the same species. Thus, although the mare as a general rule is capable of becoming pregnant while suckling, in some individuals the sexual season is postponed, the mares only becoming pregnant once in two years.

The return of menstruation during lactation in women has been dealt with recently by Heil[1] and Dingwall Fordyce.[2] Heil, who had studied the conditions of two hundred nursing mothers, expresses the belief that the occurrence of menstruation and not the condition of amenorrhœa is the normal state during lactation, but that menstruation is not so frequent in the later lactations as during the earlier ones. Fordyce has reached similar conclusions, finding that menstruation occurred during lactation in forty per cent. of the cases in which suckling was performed, while in ninety-two per cent. of the cases its return was within nine months of parturition, and that menstruation during lactation was commoner with the earlier than with the later lactations, showing that age is an important factor.

Amenorrhœa, or the absence of menstruation, may be due to anæmia or some pathological condition. Fraenkel[3] states that it was common in Germany during the recent war, when it resulted from poverty of nutrition, overwork, and strain. A condition of amenorrhœa is said to occur normally among the Esquimaux during the winter, when it is clearly comparable to the anœstrum of animals. (See also above, p. 60.)

The histological changes which occur in the internal generative organs of various Mammalia during the œstrous cycle are described at some length in the succeeding chapters.

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[1] Heil, "Laktation und Menstruation," *Monatsschr. f. Geburtsh. u. Gynäk.*, vol. xxiv., 1906.

[2] Fordyce, "An Investigation into the Complications and Disabilities of prolonged Lactation." Being an extension of papers published in *The Lancet*, Part I., 1906; *The Brit. Med. Jour.*, Part I., 1906; and *The Brit. Jour. of Children's Diseases*, 1906. Gellhorn ("Abnormal Mammary Secretion," *Jour. Amer. Med. Assoc.*, 21st November 1908) mentions a case of an ape (*Cercopithecus*) in which menstruation always disappeared during profuse lactation, but reappeared as soon as the mammary secretion ceased or became markedly decreased.

[3] Fraenkel, "Eierstockstätigkeit und Kriegsamenorrhöe," *Zent. f. Gyn.*, Jahrgang xli., 1917.

CHAPTER III

THE CHANGES THAT OCCUR IN THE NON-PREGNANT UTERUS DURING THE ŒSTROUS CYCLE

"Menstruation is like the red flag outside an auction sale; it shows that something is going on inside."—MATTHEWS DUNCAN.

FOR full descriptions of the morphology of the uterus in the different mammalian orders, reference may be made to the text-books on human, comparative, and veterinary anatomy. But before passing on to describe the changes which occur in the histology of the uterus during the menstrual cycle, it may not be out of place to remind the reader of the general structural relations of the generative organs in the human female.

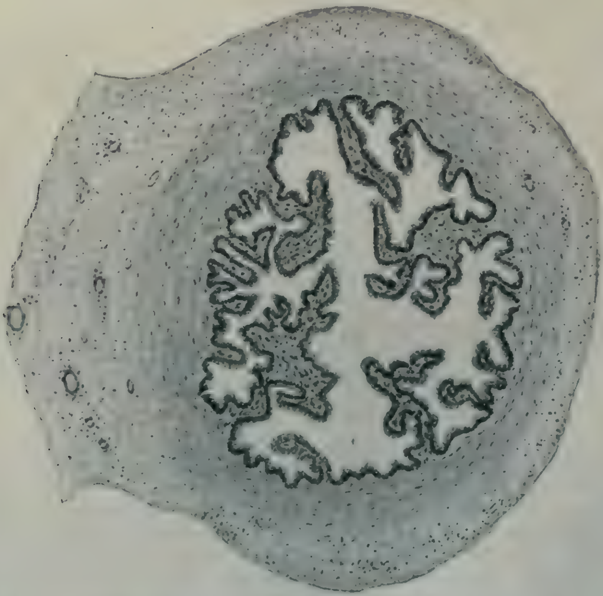

FIG. 2.—Transverse section through Fallopian tube, showing folded epithelium and muscular coat.

The two ovaries, the structure of which is described in the next chapter, are situated one on each side of the pelvis, and are connected with the posterior layer of the broad ligament of the uterus. In connection with each ovary is a Fallopian tube or oviduct, which opens into the peritoneal cavity about an inch from the ovary.[1] Surrounding the orifice is a fringe of irregular processes or fimbriæ, which, when expanded, assist in directing the ovum in its passage into the tube. The tubes are about four inches long, and terminate at the superior angles of the uterus, with the cavity of which they are in continuation. They are surrounded by an external serous coat derived from the peritoneum, a muscular coat containing both longitudinal and circular fibres, and an internal mucous membrane, which is highly vascular and is lined within by a ciliated epithelium.

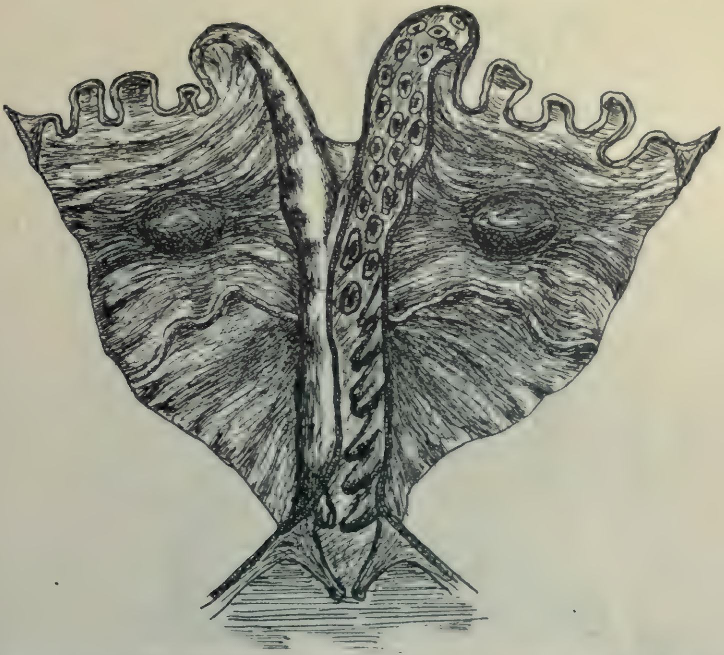

FIG. 3.—Reproductive organs of ewe, showing ovaries, Fallopian tubes, uterus, vagina, and broad ligament. The tubes at ovulation bend back towards the ovaries, and do not open outwards as represented in the figure. One of the cornua uteri and part of the corpus uteri are opened and show the cotyledonary papillæ. (L. F. Messel.)

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[1] A vestigial structure lying transversely between the ovary and the Fallopian tube on either side is called the parovarium or epoöphoron, or organ of Rosenmüller, or sometimes the duct of Gartner. It consists of a few scattered tubules, with no aperture. It is the homologue of the epididymis of the male. Vestiges of a structure corresponding to the organ of Giraldès are also sometimes found in the vicinity of the parovarium, but nearer to the uterus. These have been called the paroöphoron.

Moreaux[1] has investigated the changes undergone in the Fallopian tube of the rabbit. He finds that the epithelial cells discharge a mucous secretion during heat. The discharged eggs become surrounded by a thick mucous envelope. During the periods of rest the cells are inactive.

The human uterus consists of two parts, the corpus or body of the uterus, and the cervix or neck, which opens into the vagina. The body of the uterus contains the following layers, which correspond with those of the Fallopian tubes: (1) A serous layer; (2) a thick muscular layer, consisting of two (some say three) more or less blended sub-layers; and (3) a still thicker layer, known as the mucous membrane or mucosa (sometimes called the endometrium), which is composed of a connective tissue containing spindle-shaped cells, and is lined by a ciliated epithelium bounding the uterine cavity. The mucosa contains numerous tubular glands, which open

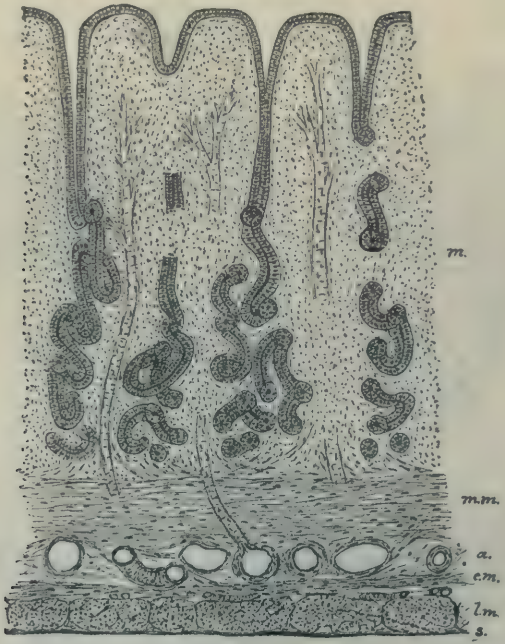

Fig. 4.—Section of a cornu of a rabbit's uterus (diagrammatic).

s, Serous layer; *lm*, longitudinal muscle fibres; *cm*, circular muscle fibres; *a*, areolar tissue with large blood-vessels; *mm*, muscularis mucosæ; *m*, mucosa. (From Schafer.)

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[1] Moreaux, "Recherches sur la Morphologie et la Fonction Glandulaire de l'Epithélium de la Trompe utérine chez les Mammifères," *Arch. d'Anat. Mic.*, vol. xiv.

out into the cavity of the uterus and are covered by an epithelial layer, these being continuous with the epithelium of the surface.[1] The sub-epithelial mucosa, which is sometimes called the uterine stroma, contains also a number of blood-vessels and lymph spaces. The vessels are branches of the ovarian and uterine arteries and veins. The uterus is also supplied by nerves which are referred to in a future chapter (p. 561).

In many of the lower Mammals the uterus is represented by two tubes, called the horns of the uterus or uterine cornua, which may unite posteriorly to form the corpus, or may, on the other hand, open separately into the vagina. The arrangement of the different layers in each of the cornua is essentially similar to that presented by the corpus uteri in the human species.

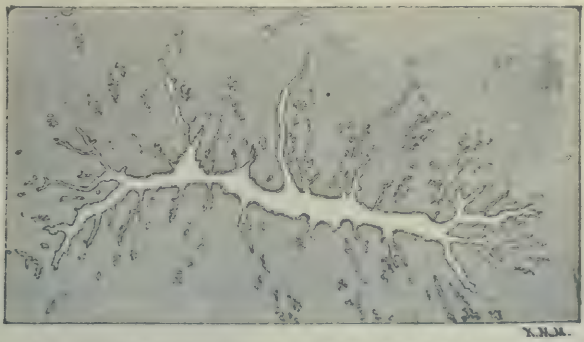

FIG. 5.—Cross-section through cervical canal of human uterus. (From Williams' *Obstetrics.* Appleton & Co.)

The neck or cervix uteri, which is narrower than the rest of the organ, opens into the vagina by a transverse aperture known as the os. The vagina is the broad passage from the uterus to the exterior. Its walls contain both longitudinally and circularly arranged muscle fibres. Internally it is lined by a stratified scaly epithelium, surrounded by erectile tissue. The entrance to the vagina from the exterior is guarded by a thin fold of mucous membrane, which usually becomes perforated at the first coition. This structure, which is called the hymen, is peculiar to the human race.[2]

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[1] With regard to the function of the glands it is clear that in their condition of greatest development (if not at other times) this is secretory in character. Witness the secretion of "uterine milk" during pregnancy (p. 432), and their comparable condition in pseudo-pregnancy. Arthur Thomson, however, has expressed the opinion that they are absorbent, and as evidence of this refers to the supposed effects of the male ejaculate (seminal fluid) upon the female (*e.g.* in promoting enlargement of thyroid). See lecture in *Brit. Med. Jour.*, 7th January 1922, "On Problems involved in the Congress of the Sexes in Man."

[2] The significance or function of the hymen is not certainly known. Metchnikoff (*The Nature of Man*, English Edition, London, 1903) suggests

The vulva comprises the female generative organs which are visible externally. These include the mons veneris, the labia major and minora, and the clitoris. The last-mentioned structure is a small erectile organ, which is homologous with the penis.[1] (See Chapter VII., p. 261.)

THE CYCLE IN MAN

In giving an account of the changes which take place in the uterus during the menstrual cycle of the human female, it will be convenient to adopt the scheme of classification employed by Milnes Marshall[2] in his work on "Vertebrate Embryology." This classification, as will be seen later, is identical with that adopted by Heape[3] in describing the menstrual changes of monkeys. The cycle is divided into four stages, as follows:—

(1) The Constructive Stage.
(2) The Destructive Stage.
(3) The Stage of Repair.
(4) The Stage of Quiescence.

The last stage may conveniently be considered first.

The Stage of Quiescence.—The normal condition of the human endometrium has been described by Webster,[4] to whose account the reader is referred. This author calls special attention to the following points: (1) The thickness of the mucosa is not uniform, but varies considerably. (2) The epithelial cells which line the mucosa, and also those which line the glands, show differences in shape and size, and in the position of the nuclei. (3) The epithelial cells lining the glands are, as a rule, larger than the superficial cells. (4) The interglandular connective tissue or stroma is mainly embryonic in nature, and consists of a nucleated protoplasmic reticulum, containing every stage of transformation into the more differentiated spindle-shaped cells. (5) The stroma nearest the

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that it may have been useful in the earlier history of the race, when sexual intercourse probably occurred at an early age, before the reproductive organs were mature. Under such circumstances the hymen, instead of being a barrier, may have facilitated successful coitus. Metchnikoff supposes the aperture to have become gradually dilated by repeated intercourse without being torn, until it admitted of the entrance of the adult male organ.

[1] The triangular space above the orifice of the vagina into which the female urethra opens is often called the vestibule.

[2] Milnes Marshall, *Vertebrate Embryology*, London, 1893.

[3] Heape, "The Menstruation of Semnopithecus, etc.," *Phil. Trans.*, B., vol. clxxxv., 1894, and vol. clxxxviii., 1897. A similar classification has been adopted by Minot (*Human Embryology*, 1892), who divides the menstrual process into (1) Tumefaction; (2) Menstruation; and (3) Restoration of the mucosa.

[4] Webster, *Human Placentation*, Chicago, 1901.

surface is for the most part arranged parallel to it, the cells immediately below the epithelium forming a kind of basement-membrane. (6) The superficial portion of the mucosa is supplied only by capillaries. (7) The line of junction of mucosa and muscle-wall is irregular, and there is no special muscularis mucosæ. Whether the human uterus is really ever in a state of rest is open to question, since there is no anœstrum, and the constructive stage follows very rapidly if not immediately upon the stage of repair.

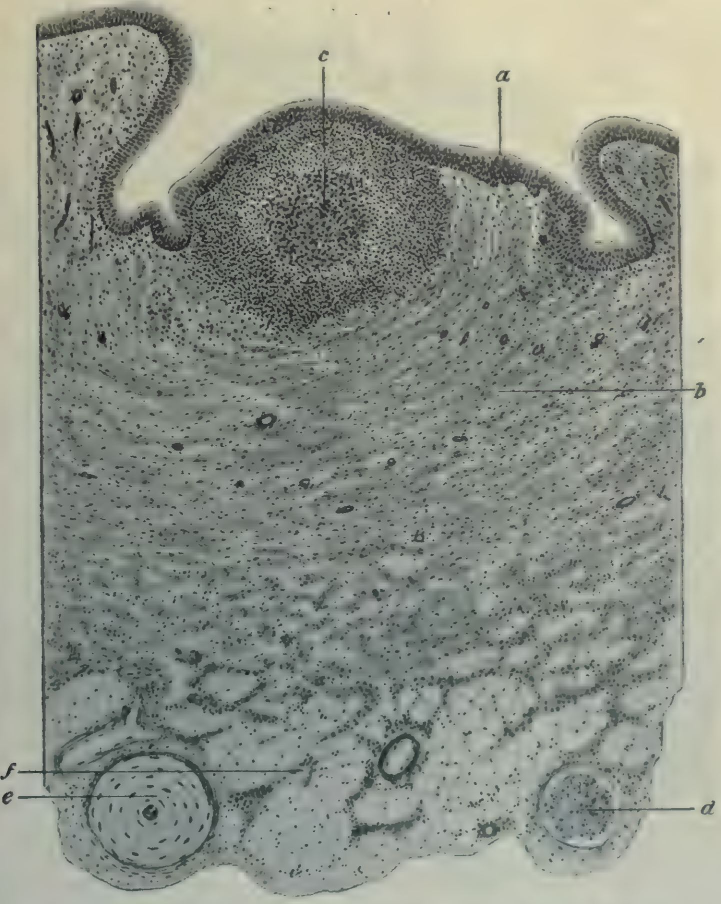

Fig. 6.—Section through wall of vagina (upper part) of monkey. *a*, Epithelium ; *b*, sub-mucous layer ; *c*, lymphatic gland ; *d*, nerve ; *e*, Pacinian body ; *f*, fat cells.

The Constructive Stage.—During this stage the stroma of the uterus undergoes a process of growth. This is brought about partly by cell division, partly (according to Engelmann[1]) by an increase in intercellular substance, and partly by an enlargement of the glands and blood-vessels. According to Lipes,[2] this stage commences as soon as the process of regeneration (following the preceding menstrual period) is completed, which is about eighteen days after the cessation of the previous flow. "During the stage of regenera-

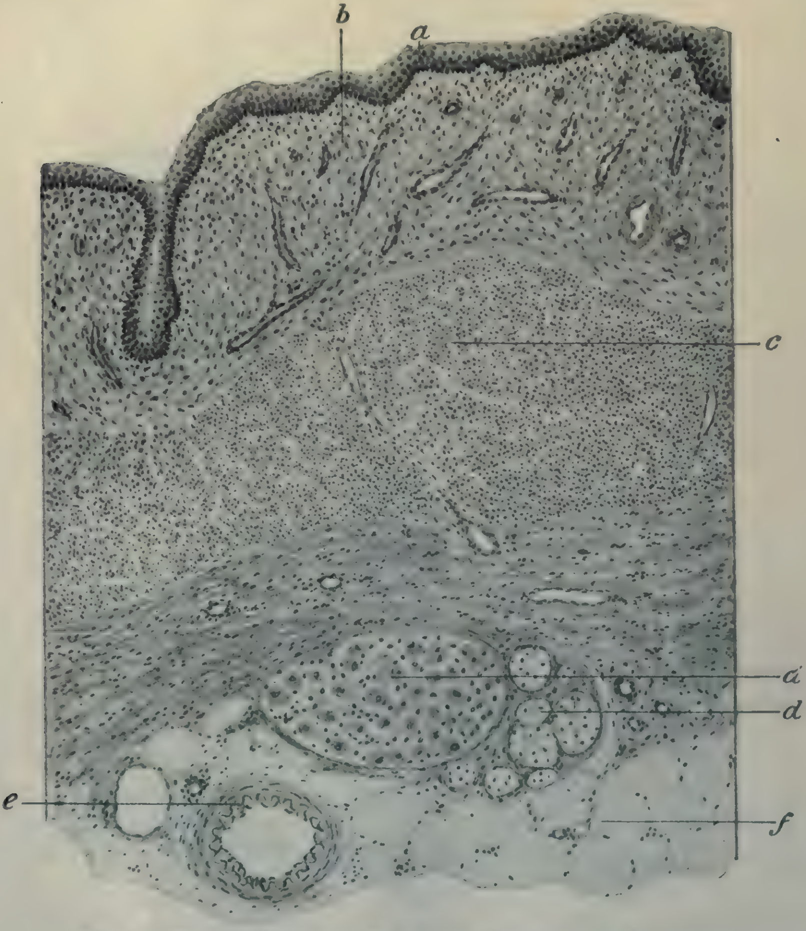

FIG. 7.—Section through wall of vagina (lower part) of monkey. *a*, Epithelium lining cavity ; *b*, sub-mucous layer ; *c*, muscular layer ; *d*, *d′*, nerve ganglia ; *e*, artery ; *f*, fat cells.

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[1] Engelmann, "The Mucous Membrane of the Uterus, etc.," *Amer. Jour. Obstet.*, vol. viii., 1875.

[2] Lipes, "A Study of the Changes occurring in the Endometrium during the Menstrual Cycle," *Albany Medical Annals*, vol. xxv., 1904.

tion the cells of the stroma lay over each other rather thickly, but now become pressed apart, particularly in the outer third of the mucosa. The protoplasm of these cells becomes compressed, and the projections by which they are bound together are either greatly lengthened or completely separated." The capillaries of the mucous membrane become congested (Fig. 8), and a serous or sanguineo-serous exudate infiltrates into the stroma. The enlargement of the vessels continues, but does not become very pronounced until shortly before the stage of destruction which may be said to mark the beginning of menstruation proper.

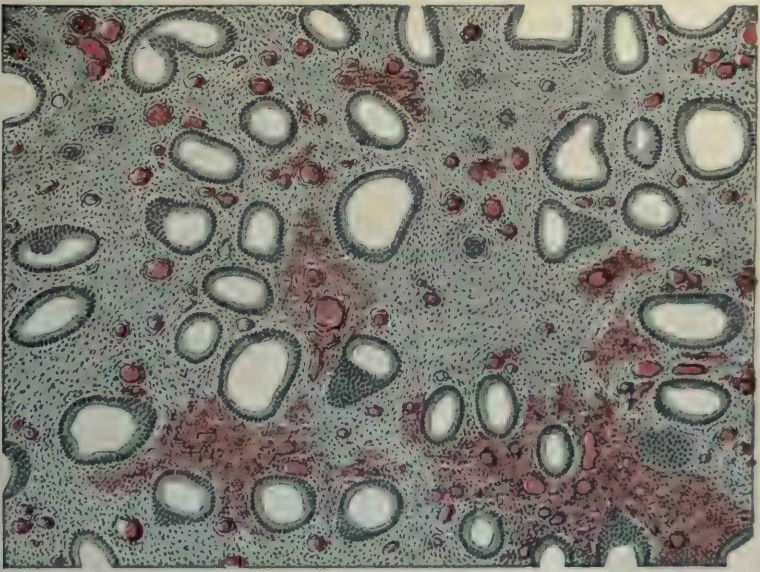

Fig. 8.—Section through mucosa of human uterus, showing pre-menstrual congestion. (From Sellheim.)

Lipes also describes an increase in the size of the glands of the mucous membrane, which he supposes to be due to the collection of the secretion of the gland-cells. This mucus-like product of the gland-cells is said to give them a distinctly granular appearance. "The gland-cells become uniformly swollen and take stains more evenly, and their nuclei are more widely separated as a result of the increase in the volume of the protoplasm, and are uniformly more round in comparison with the oval nuclei, which are seen in the regeneration period." Westphalen[1] has pointed out that the nuclei, which are situated near the base of the cell as a rule, appear in the middle of the cell at the beginning of the stage of pre-menstrual swelling.

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[1] Westphalen, "Zur Physiologie des Menstruation," *Arch. f. Gynäk.*, vol. lii., 1896.

As a consequence of these changes the mucosa becomes considerably increased in thickness. Thus, if a woman who had been menstruating regularly dies shortly before the expected approach of a menstrual period, the thickness of the mucous membrane is often as much as one-sixth of an inch at its thickest part, as compared with a thickness of from one-tenth to one-twentieth of an inch in women who died within ten days after the cessation of the flow.[1] Leopold[2] has described a growth so considerable that the uterine cavity, prior to the stage of bleeding, becomes almost completely obliterated.

It should be mentioned, however, that according to some authors the amount of pre-menstrual growth in the uterine mucosa is very slight, while Oliver[3] seems to be doubtful whether any growth occurs at all, stating that he has made an examination of uteri at various pre-menstrual and menstrual stages, and has failed to find any evidence of changes in the mucosa tissue apart from those directly associated with the phenomena of bleeding. Westphalen's view appears to be similar; for, according to this observer, there is no multiplication of nuclei during this stage, the pre-menstrual swelling being brought about entirely by the serous saturation of the stroma.

The Destructive Stage.—At the close of the constructive period the blood leaves the capillaries and becomes extravasated freely in the stroma, but there has been some dispute as to how this process is effected. It has been suggested that the blood transudes through the walls of unruptured capillaries under the influence of congestion, or that permanent openings exist from the vessels into the uterine glands, these being closed normally by muscular contraction;[4] but the belief now generally held is that, whereas the walls of many of the congested vessels break down under pressure, and so freely admit of the exit of the blood corpuscles into the mucosa tissue, hæmorrhage also takes place partly by diapedesis. Engelmann,[5] Williams,[6] and others have ascribed the breaking down of the vessel-walls to fatty degeneration, but this has been denied by Möricke,[7] and more recently by Findley,[1] while Leopold has described the appearance of the fatty degeneration as a result rather than a cause of hæmorrhage.

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[1] Galabin, *A Manual of Midwifery*, 6th Edition, London, 1904.

[2] Leopold, "Untersuchungen über Menstruation und Ovulation," *Arch. f. Gynäk.*, vol. xxi., 1883.

[3] Oliver, "Menstruation: its Nerve Origin," *Jour. Anat. and Phys.*, vol. xxi., 1887.

[4] Galabin, *loc. cit.*

[5] Engelmann, *loc. cit.*

[6] Williams (Sir J.), "The Mucous Membrane of the Body of the Uterus," *Obstet. Jour. Gt. Britain*, vols. iii. and v., 1875, 1877.

[7] Möricke, "Die Uterusschleimhaut in der verschiedenen Altersperioden und zur Zeit der Menstruation," *Zeitsch. f. Geburtshülfe u. Gynäk.*, vol. vii., 1882.

After the extravasation of blood, the corpuscles tend to become aggregated in lacunæ which lie beneath the superficial epithelium. These lacunæ are the sub-epithelial hæmatomata of Gebhard,[2] according to whom the epithelium becomes lifted almost bodily from its bed, the space between it and the stroma being filled with blood. Gebhard concludes that the blood eventually reaches the uterine cavity by being forced between the epithelial cells, or that a larger exit is provided by certain of the cells being carried bodily away. Gebhard also believes that bleeding may take place into the lumina of the glands. Christ[3] states that when the menstrual flow is very profuse there is a considerable loss of surface epithelium, but that in other cases the removal of epithelium is slight. This author has also described bleeding into the glands. (Fig. 10.)

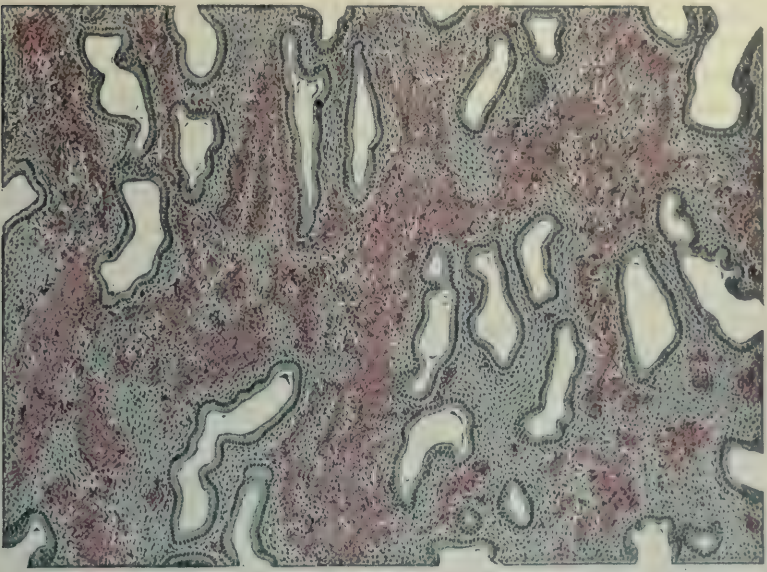

FIG. 9.—Section through mucosa of human uterus, showing extravasation of blood. (From Sellheim.)

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[1] Findley, "Anatomy of the Menstruating Uterus," *Amer. Jour. Obstet.*, vol. xlv., 1902.

[2] Gebhard, "Ueber das Verhalten der Uterusschleimhaut bei der Menstruation," *Verhand. d. Gesells. f. Geb. u. Gyn. zu Berlin*, *Zeitsch. f. Geb. u. Gyn.*, vol. xxxii., 1895.

[3] Christ, "Das Verhalten der Uterusschleimhaut während der Menstruation," *Inorg. Dissert.*, Giessen, 1892.

Very contradictory statements have been made regarding the extent to which denudation takes place during menstruation. Williams (Sir J.), von Kahlden,[1] and others among the older writers, expressed the belief that a large part, if not the whole, of the uterine mucous membrane was destroyed. This view, as will be seen later, has been partially confirmed for monkeys by Heape. It has been pointed out, however, by Whitridge Williams,[2] that the older writers made their observations upon uteri which had undergone post-mortem changes. The preponderance of recent opinion appears to be that destruction of the mucous membrane is, as a rule, confined to the epithelium, and that this is only partially removed. Among those who have accumulated evidence in support of this conclusion are Gebhard, Strassmann,[3] Westphalen, Findley, Whitridge Williams, and Lipes. De Sinety,[4] Möricke, and Oliver appear to uphold the opinion that even the superficial epithelium remains practically intact. Mandl,[5] Maerdervort,[6] and also Champneys[7] have made the exceedingly likely suggestion that the extent to which the mucosa is destroyed varies within wide limits in different individuals or even in the same individuals at different periods of life. "Exfoliation dysmenorrhœa" (see p. 61) is probably a condition caused by a more extensive denudation of the superficial layers of the mucosa than occurs usually during menstruation.[8] Oliver, who maintains that menstruation is essentially a secretory process, states that in cases of chronic inversion of the uterus there is no denudation of epithelium during menstruation.[9]

Minot[10] and Martin,[11] agree in supposing that the superficial layers of the mucosa degenerate after the blood has passed out, so that the bleeding is in no sense the consequence of the destruction. According to Martin, fatty degeneration plays a distinct part in causing the destruction.

Lipes has shown that the amount of destruction is related to the character of the hæmorrhage. If the congestion is rapid and the amount of extravasated blood large, the denudation is comparatively extensive; but if the hæmorrhage is slight, and takes place chiefly by diapedesis, then the loss of tissue is practically *nil.* Lipes adds that in none of the cases examined by him were there enough epithelial cells in the discharge to suggest a complete loss of epithelium.

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[1] Von Kahlden, "Ueber das Verhalten der Uterusschleimhaut während und nach der Menstruation," *Hegar's Festschrift*, Stuttgart, 1889.

[2] Whitridge Williams, *Obstetrics*, London and New York, 1904.

[3] Strassmann, "Beiträge zur Lehre von der Ovulation, Menstruation, und Conception," *Arch. f. Gynäk.*, vol. lii., 1896.

[4] De Sinety, "Recherches sur la muqueuse utérine pendant la menstruation," *Annales de Gynæc.*, 1881.

[5] Mandl, "Beitrag zur Frage des Verhaltens der Uterusmucosa während der Menstruation," *Arch. f. Gynäk.*, vol. lii., 1896.

[6] Maerdervort, "Die normale und menstruirende Gebärmutterschleimhaut," *Inorg. Dissert.*, Freiburg, 1895.

[7] Champneys, "On Painful Menstruation," *Harveian Lectures*, 1890.

[8] Blair Bell, *The Principles of Gynæcology*, London, 1910.

[9] Oliver, *New York Med. Jour.*, August 1906, June 1907, and November 1920.

[10] Minot, *loc. cit.*

[11] Martin, "The Physiology of Ovulation, Menstruation, and Fertilisation," Hirst's *Obstetrics*, vol. i., 1888.

Galabin states that in addition to uterine and vaginal epithelial cells being found in the discharge, shreds of tissue can frequently be detected showing the structure of uterine stroma. Heape[1] also has detected stroma tissue in the menstrual discharge of the human female. This clearly shows that destruction is not always confined to the epithelial layer.

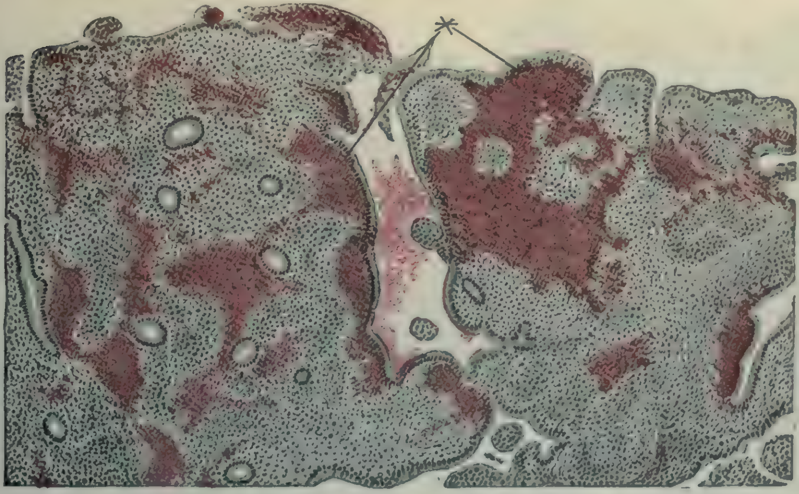

FIG. 10.—Section through mucosa of human uterus, showing sub-epithelial hæmatomata *. (From Sellheim.)

The blood poured out into the uterine cavity, and thence to the exterior, does not usually clot, unless the amount be excessive. This is probably due to the absence of fibrin ferment, and perhaps also to the fact that the blood is considerably diluted with mucus derived from the uterine glands. The glandular activity is accompanied by an emigration of leucocytes which, according to Blair Bell,[2] are engaged in excreting calcium compounds (see p. 63). The relative proportion of blood to mucus in the fluid is usually said to increase from the commencement of menstruation, until the discharge reaches its maximum, after which it goes on diminishing until the flow ceases. Oliver[1] has made a quantitative examination of the menstrual fluid obtained from a girl with an imperforate hymen. After making an incision he withdrew 70 oz.: 87·13 per cent. was water; of the remainder 4·98 per cent. was ash and 95·02 organic material, including 12·49 serum albumen, 16·56 globulin, 3·37 mucin, and a trace of fat. The ash contained sodium, potassium, calcium, phosphorus, and iron; and the salts, chlorides, carbonates, phosphates, and sulphates.

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[1] Heape, "The Menstruation and Ovulation of Monkeys and the Human Female," *Trans. Obstet. Soc.*, vol. xl., 1899.

[2] Blair Bell, "Menstruation and its Relation to the Calcium Metabolism," *Proc. Roy. Soc. Med.*, July 1908.

The Stage of Repair.—This corresponds to Gebhard's period of post-menstrual involution. After the flow has ceased, or even a short time before it has quite ceased, regeneration of the uterine mucosa begins. According to Westphalen,[2] profuse karyokinesis takes place in the tissue of the mucosa, which once more increases in thickness, whereas Heape, as will be seen later, describes a shrinkage as occurring in the regenerative stage in monkeys. Wyder,[3] who believed in the partial destruction of the uterine stroma, concluded that this was restored by a hyperplasia of cells in the interglandular tissue of the deeper layers of the mucous membrane, and that the lost epithelium was regenerated from the epithelium of the glands. Similar views have been held by other writers.

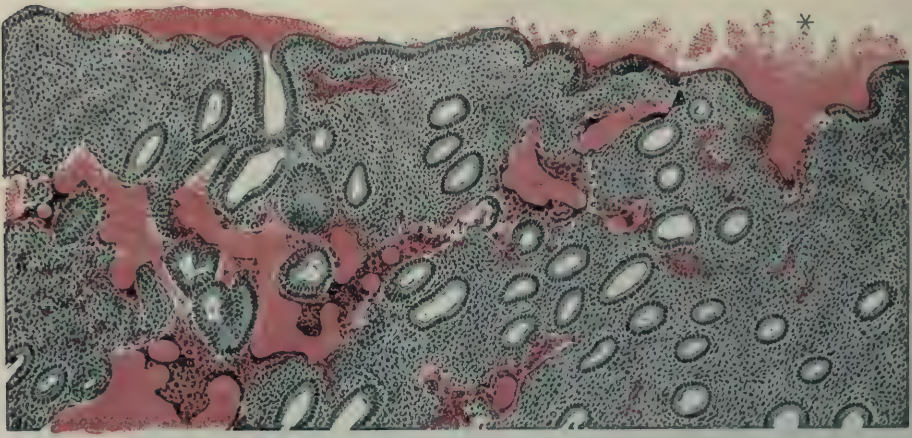

Fig. 11.—Section through mucosa of menstruating human uterus, showing bleeding into the cavity *. (From Sellheim.)

Those authorities who hold that the destruction is practically confined to the epithelium believe that the lost cells are replaced by multiplication of the remaining cells. Mandl, for example, describes various stages of mitotic division in the cells of the epithelium at this stage. But this author is of opinion that the epithelia of the glands assist in the process of renewal. Gebhard describes the epithelium, which had been lifted from its bed by the blood in the hæmatomata, as sinking back to its former position, such cells as were lost being regenerated by multiplication of the others.

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[1] Oliver, "New Aspects of Menstruation," *New York Med. Jour.*, November 1920.

[2] Westphalen, *loc. cit.*

[3] Whitridge Williams, *loc. cit.*

The restoration of the mucosa is accompanied by a decrease in the size of the blood-vessels, and an absorption of the blood which remains extravasated in the stroma. As to how the blood is absorbed has not been determined in the human female. This is a question which will be discussed in considering the regeneration stage in monkeys and in the lower Mammals. It is stated that new capillaries are formed after the close of the destruction.[1]

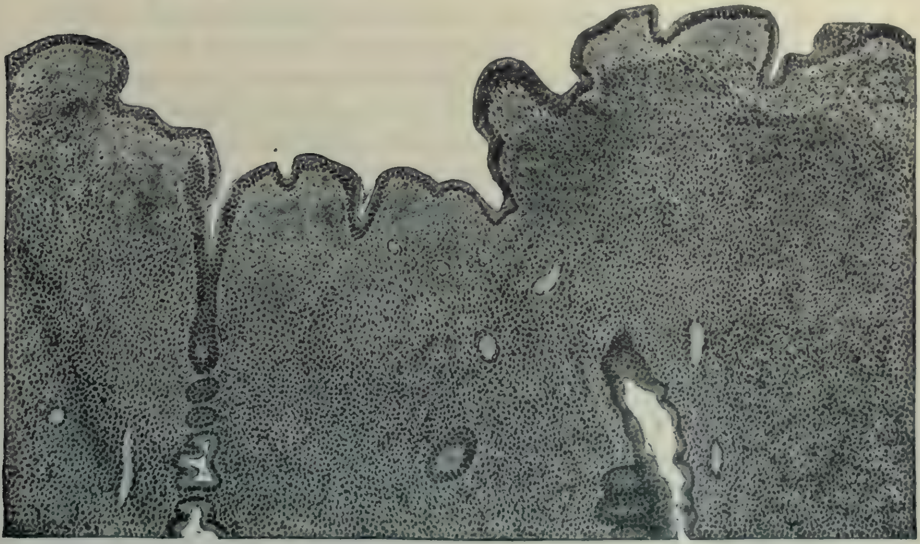

FIG. 12.—Section through the human uterus during the recuperation stage. (From Sellheim.)

It has already been mentioned that, according to Lipes,[2] the constructive stage commences as soon as repair is completed. There is undoubtedly glandular development which may possibly be comparable to what occurs during the post-œstrous or pseudo-pregnant period in the bitch (see below, p. 98). In this connection it is interesting to note that, according to Hitschmann and Adler,[1] the pre-menstrual uterus in man undergoes changes which are similar in character to those observed in the pregnant uterus. It seems possible, therefore, to regard menstruation in man as representing pseudo-pregnant destruction (see pp. 107 and 156) as well as prœstrous degeneration, the two series of changes being here telescoped into one month.[2]

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[1] Geist, "Untersuchungen über die Histologie der Uterusschleimhaut," *Arch. f. Mikr. Anat.*, vol. lxxxi., 1913. See also Coryllos, *Revue de Gynæcol.*, vol. xviii. and vol. xxvii.

[2] Lipes, *loc. cit.*

The average length of the normal menstrual cycle, as already mentioned, is twenty-eight days. Of these about five are occupied by the pre-menstrual swelling, four by menstruation, and probably about seven by the regeneration process, leaving not more than twelve days for the period of quiescence.[3] There can be no doubt, however, that the length of the respective stages must vary according to the extent of the destruction and the amount of tissue which it is necessary to replace. According to Westphalen,[4] the regenerative process may last for as long as eighteen days, or until the commencement of the succeeding pre-menstrual swelling.[5]

THE CYCLE IN MONKEYS

The histology of the menstrual cycle in *Semnopithecus entellus* and *Macacus rhesus* has been very fully studied by Heape.[6] Previously to Heape's work, Bland Sutton[7] had paid some attention to the histology of the menstrual process in *Macacus rhesus*, but without entering into great detail. More recently van Herwerden[8] has given an account of the cyclical changes of the uterus in *Cercocebus cynomolgus*.

Heape has divided the cycle into the following four periods and eight stages :—

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[1] Hitschmann and Adler, "Der Bau der Uterusschleimhaut des Geschlechtsreifen Weibes," *Monatschr. f. Geb. u. Gynäk.*, vol. xxvii., 1908.

[2] Marshall and Halnan, "On the Post-Œstrous Changes occurring in the Generative Organs and Mammary Glands of the Non-Pregnant Dog," *Proc. Roy. Soc.*, B., vol. lxxxix., 1917.

[3] Whitridge Williams, *loc. cit.*

[4] Westphalen, *loc. cit.*

[5] For further references to the subject of menstruation in the human female the following authors may be consulted: Steinhaus, *Menstruation and Ovulation*, Leipzig, 1890; Heape, *Phil. Trans.*, B., vols. clxxxv. and clxxxviii., 1894 and 1897; Gebhard, "Die Menstruation," *Veit's Handbuch der Gynäk.*, vol. iii., 1898. For an account of the various pathological changes which are known to occur in the human uterus, see Macgregor, *A Contribution to the Pathology of the Endometrium*, Edinburgh, 1905.

[6] Heape, *loc. cit.*

[7] Bland Sutton, "Menstruation in Monkeys," *Brit. Gynæc. Jour.*, vol. ii., 1880.

[8] Van Herwerden, "Bijdrage tot de Kennis van den Menstrueelen Cyclus," *Tijdschrift. d. Ned. Dierk. Vereen.*, vol. x., 1906.

A. Period of Rest.	Stage	I. The Resting Stage.
B. Period of Growth.	,,	II. The Growth of Stroma.
	,,	III. The Increase of Vessels.
C. Period of Degeneration.	,,	IV. The Breaking Down of Vessels.
	,,	V. The Formation of Lacunæ.
	,,	VI. The Rupture of Lacunæ.
	,,	VII. The Formation of the Menstrual Clot.
D. Period of Recuperation.	,,	VIII. The Recuperation Stage.

Heape's account may now be briefly summarised.

I. *The Resting Stage.*—The epithelial layer of the uterine mucosa consists of a single row of cubical or columnar cells. The outer border is clearly defined, but on the inner side the protoplasm of the epithelium is continuous with that of the sub-epithelial mucosa or stroma tissue. The surface epithelium is continuous with that of the glands, but the latter rest on a basement-membrane which separates them from the interglandular stroma. The stroma contains round nuclei embedded in a network of protoplasm, with fine, delicate processes in which granules may be seen. In *Semnopithecus* fibrils running fan-wise were observed in the deeper parts of the stroma, but these were not seen in *Macacus*. Multiplication of cells was not noticed at this stage, either in the epithelium or in the stroma. The vessels in the mucosa are small. A few arteries occur in the deeper portion, but only thin-walled capillaries in the more superficial part; the latter, however, are fairly numerous.

II. *The Growth of Stroma.*—The nuclei of the more superficial part of the stroma undergo a great increase, the division being amitotic in character, at least so far as could be seen. As a consequence the mucosa in its upper third becomes considerably swelled (hyperplasia), but in the deeper portion there is no change in the tissue. Owing to the effects of pressure the nuclei become elongated or fusiform. Division occurs either by fragmentation or by the nucleus simply splitting into two. The growth in the upper part of the stroma is associated with an increase in the size of the blood-vessels in the deeper part. The superficial epithelium, and also the epithelium of the glands, remain practically unchanged.

III. *The Increase of Vessels.*—Owing to the continued swelling of the stroma the nuclei in the superficial portion are packed less densely, the lining epithelium becoming simultaneously stretched. The glands tend to become wider. Hyperplasia of the vessels occurs below the epithelium, the surface of the mucosa appearing flushed. At the same time leucocytes become more numerous within the vessels. There is no change in the constitution of the deeper portion of the stroma.

IV. *The Breaking Down of Vessels.*—The whole of the mucosa, including the epithelium, stroma, and vessel-walls, undergoes pronounced hypertrophy, and in the superficial region the congested capillaries break down and their contents become extravasated through the stroma. Fatty degeneration was not observed by Heape, who is disposed to think that the degeneration is of the amyloid or hyaline type. The leucocytes were noticed to be increased decidedly in number, but they were only detected outside of the blood-vessels in the superficial stroma, where the vessel-walls had given way. Diapedesis of corpuscles was nowhere observed. The nuclei of the stroma become larger and more rounded, and exhibit a nuclear network and deeply staining nucleoli. The glands increase in size, becoming longer; their lumina are wide, and an active process of secretion is taking place. Superficially the mucosa appears very markedly flushed.

V. *The Formation of Lacunæ.*—At this stage the extravasated blood corpuscles collect in lacunæ which are situated in the loose stroma tissue which lies below the epithelium. These lacunæ are clearly identical with the sub-epithelial hæmatomata of Gebhard. The dense stroma tissue, characteristic of an early stage, still persists in places, but is now of rare occurrence. All the superficial vessels have by this time broken down, but those in the deeper tissue remain intact. Neither leucocytes nor red corpuscles are to be found free in the deeper tissue of the stroma. The condition of the glands is the same as in the preceding stage, but there is evidence of degenerative changes in certain of the stroma nuclei, and also in some of the free leucocytes.

VI. *The Rupture of Lacunæ.*—The superficial stroma and epithelium shrivel up at this stage, and, as a consequence, the blood contained in the lacunæ is poured into the uterine cavity. The lacunæ are very often close to the glands, so that when a lacuna ruptures, a whole gland may be carried away in the blood-stream. The lacunæ have no regular inner wall, but in some places the processes of the stroma were observed to combine together to form a kind of wall which appeared to resist the further encroachment of blood corpuscles in the stroma tissue. Leucocytes are very numerous (usually in the close neighbourhood of the ruptured vessels), some of them being described as mononuclear, and some as having two, three, or four nuclei (products of division). The proportion of leucocytes to red corpuscles was found to be 2 per cent. of the former to 98 per cent. of the latter in unruptured vessels full of blood, while in ruptured vessels, from which blood had escaped, the percentage of leucocytes was noted to be as high as 18·75. Heape does not state, however, that basophil or eosinophil cells occur, such as have been described in the uterus of the dog at a corresponding stage in the cycle. Degenerative changes were noted in many of the epithelial cells, and also in some of the stroma cells, certain of which were seen scattered beneath the remains of the epithelial lining. The stroma below the lacunæ was observed to contain normal as well as shrivelled tissue, but the deeper parts appeared to undergo very little alteration.

VII. *The Formation of the Menstrual Clot.*—At this stage Heape describes "a severe, devastating, periodic action." The entire superficial epithelium, portions of the glands or even a whole gland, and a part of the stroma, with broken-down blood-vessels and corpuscles, are torn bodily away, "leaving behind a ragged wreck of tissue, torn glands, ruptured vessels, jagged edges of stroma, and masses of blood corpuscles, which it would seem hardly possible to heal satisfactorily without the aid of surgical treatment." Heape is in no doubt as to the extent of the denudation, differing thus from those writers referred to above, who believe that the destructive process in the human female does not extend beyond certain portions of the superficial epithelium. The cast-off mucous membrane is termed by Heape the mucosa menstrualis. The deeper tissue undergoes no change, the blood-vessels therein being still possessed of complete walls, but these are larger and more numerous than before. There is no extravasated blood in this region. The proportion of leucocytes in the vessels was observed to be about three per cent. of the corpuscles present, while those on the surface were estimated to comprise about 2·5 per cent. of the total number of corpuscles. Heape ascribes this comparative equalisation to the fact that the ruptured vessels to which the leucocytes adhered in the earlier stages, are themselves cast off, and their contents mingled with the extravasated blood. The supply of leucocytes in the vessels, however, is well maintained.

The menstrual discharge is described as consisting of (1) a viscid, stringy, opaque white fluid derived partly from the blood-serum and partly from the secretion of the uterine glands, containing numerous small granules which have their origin in the broken-down plasmodium of the uterine mucosa; (2) red blood corpuscles; (3) masses of stroma tissue and epithelium, both from the lining of the uterine cavity and from the glands, and squamous epithelium from the vagina; and (4) leucocytes together with isolated nuclei of broken-down epithelial and stroma cells. The menstrual clot is composed very similarly, containing a mass of corpuscles together with fragments of uterine tissue. It is expelled at the end of menstruation after remaining some time in the uterine cavity.

VIII. *The Recuperation Stage.*—The changes which occur during this stage are described by Heape as consisting of five processes, as follows:—

(1) The re-formation of the epithelium.
(2) The reduction of the blood supply.
(3) The formation of new and recuperation of old blood-vessels.
(4) The changes which take place in the stroma.
(5) The behaviour of the leucocytes.

(1) The new epithelium is formed, according to Heape, partly from the epithelium of the glands, but partly from the underlying stroma. The latter is described as a tissue of very primitive characteristics, and the re-formation of the epithelium is regarded as a specialisation of cells belonging to a layer which, in the embryo, gave rise in the same way to similar epithelial cells (that is to say, on this view, what takes place after menstruation is merely a repetition of a process which occurs in the embryo). The new epithelial cells, which are at first flattened, gradually become cubical. Heape's account is thus completely at variance with the descriptions of those authors who hold that in the human female the epithelium is renewed entirely from the torn edges of the old epithelium. Heape states that the process of re-formation commences before the expulsion of the menstrual clot, and even before the cessation of the flow of blood into the uterine cavity.

(2) There is still an escape of blood as long as the menstrual clot lies within the uterine cavity, but after its expulsion the flow is checked. Heape suggests that the contractions of the uterus which serve to expel the clot may assist in stopping the escape of blood. Probably, also, the growth of the new epithelium helps to stop the hæmorrhage. After the growth of the new vessels the flow of blood entirely ceases.

(3) At the commencement of this stage many of the extravasated blood corpuscles are seen lying in intercellular spaces in the stroma. These corpuscles, according to Heape, are drawn again into the circulatory system by becoming enclosed within newly formed capillaries. Heape describes the process as follows: "The protoplasm of the cells bounding these [blood-containing] spaces flattens out, the nuclei of the cells becoming also flattened and elongated, and numerous fine capillary vessels are thus formed, continuous with the deeper parts of the mucosa with large pre-existing capillaries, and so with the circulatory system.

"These fine capillaries exist only temporarily. When the blood corpuscles are again drawn into the circulation, and when the mucosa has shrunk again into its resting condition, the fine capillaries are no longer seen; but during the time in which the reclaiming process goes on they exist in very large numbers." It should be added that this description of the formation of vessels in the uterine mucosa of *Semnopithecus* and *Macacus* is in opposition to the usual view regarding the growth of new vessels, which are ordinarily supposed to be only capable of developing as off-shoots from pre-existing ones.

Heape also describes a recuperation of the old blood-vessels. The nuclei which were hypertrophied become reduced in size, and the swollen protoplasm becomes contracted. In this way the vessels are reduced once more to their normal size.

(4) The changes in the cells of the stroma are described as being similar to those in the cells which form the walls of the hypertrophied vessels, the large nuclei and swollen protoplasm giving place to compact nuclei and fine thread-like processes of protoplasm. The multiplication of the stroma nuclei still goes on to a limited extent, but is not nearly so frequent. The tissue is very open during the early stages of recuperation, but gradually becomes drawn together. As a result the whole stroma is reduced considerably in bulk.

(5) The extravasated leucocytes, like the red corpuscles, are said to be returned into the circulatory system by means of the newly formed vessels. Heape says that isolated wandering leucocytes are very rare indeed at this stage, and he makes no mention of basophil or eosinophil cells, such as have recently been described in the uterus of the dog. The actual proportion of leucocytes within the vessels is said to be greater than at any other period in the cycle, as many as fifty per cent. having been observed in certain of the vessels. With regard to the function of the leucocytes Heape suggests that in cases of suppressed menstruation they might play an important part, but that in normal menstruation "they seem to have been induced to appear on the scene in such numbers, unnecessarily; the casting away of the menstrual mucosa, together with all noxious material, and the clean healing of the wounded surface, rendering their protective presence unnecessary." At the same time Heape points out that the presence of the leucocytes in the vessels is evidence of the existence therein of a noxious substance which is not present in the surrounding tissue, and he supposes that this irritant may be got rid of completely in the flow of blood.

Menstruation in *Macacus* has also been studied by Bland Sutton,[1] according to whom the sanguineous discharge is slight. Sutton found no evidence of destruction of the uterine mucosa, not even of the epithelium, but the uterus was distinctly congested, and there was an escape of blood into the cavity. It should be noted, however, that Sutton's investigation was upon monkeys in this country, whereas Heape's observations relate to Indian animals, and that in Pocock's experience,[1] menstruation does not, as a rule, occur in *Macacus rhesus* in the Zoological Gardens. But it would appear also from this author's observations that the severity of the menstrual process in monkeys may vary within as wide limits as it is said to do in the human female.

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[1] Bland Sutton, "Menstruation in Monkeys," *Brit. Gynæc. Jour.*, vol. ii., 1880.

The changes which occur throughout the menstrual cycle in *Cercocebus cynomolgus* have been studied in some detail by van Herwerden,[2] who begins by classifying the material in two groups. In group A are included those animals in which, at the time of killing, the uterus was relatively small and menstruation was correspondingly slight. In group B are placed those monkeys which, on being killed, showed comparatively large well-developed uteri, and in which the menstrual process was characterised by some degree of severity. Van Herwerden is of opinion that the individuals included in the first category were animals killed during the non-breeding season, while those belonging to group B were specimens killed at the breeding season, when the generative organs were in a state of greater activity.

The complete menstrual cycle in *Cercocebus* is divided into the following periods and stages:—

- I. Inter-menstrual period.
- II. Pre-menstrual period -
  - 1. Increase of superficial stroma elements.
  - 2. Slight swelling of mucosa.
- III. Menstrual period -
  - 1. Increasing hyperæmia.
  - 2. Rupture of capillaries.
  - 3. Formation of lacunæ.
  - 4. Degeneration of epithelium and stroma elements.
  - 5. Rupture of lacunæ and tearing off of degenerate tissue.
  - 6. Beginning of regeneration.
- IV. Post-menstrual period.

It will be seen from this scheme of classification that the changes recorded by van Herwerden as occurring in the menstrual cycle of *Cercocebus* are very similar to those described by Heape in *Semnopithecus* and *Macacus*. Both authors agree in stating that the superficial portion of the mucosa is denuded during the destruction period, differing thus from Bland Sutton and those writers on human menstruation (referred to above) who maintain that the denudation only involves certain portions of the superficial epithelium. Van Herwerden states that the menstrual changes are less marked in the region of the fundus uteri.

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[1] Pocock, "Notes upon Menstruation etc.," *Proc. Zool. Soc.*, 1906.

[2] Van Herwerden, *loc. cit.*

The chief differences between van Herwerden's account and that of Heape are as follows:—

According to the former the stroma cells increase mitotically, and not by simple division or fragmentation as supposed by Heape.

The epithelium is described as being renewed from the glandular epithelium in *Cercocebus*, and not in part from the subjacent stroma, as it is said to do in *Semnopithecus* and *Macacus*.

Van Herwerden says that, so far as was observed, the walls of new vessels were not formed during recuperation from stroma cells as has been described by Heape.

Van Herwerden states that *Cercocebus* may experience œstrus after menstruation is over. Presumably, therefore, œstrus occurs contemporaneously with the recuperation process in the uterus.

The Cycle in Lemurs

As already mentioned, Stratz[1] has called attention to the proœstrous changes which take place in the uterus of *Tarsius spectrum*, but the process has been studied more closely by van Herwerden.[2] This author describes the following changes:—

(1) There is a swelling of the glands which is closely followed by mitotic division among a large number of the epithelial cells. Hyperæmia then sets in; but the congestion is localised to certain places, and is not diffused over the entire mucous membrane. Afterwards blood becomes extravasated in the stroma tissue, the corpuscles being aggregated in the more superficial parts—that is to say, in the vicinity of the epithelium. It was noticed that certain corpuscles were taken up by leucocytes, and transported to the uterine cavity. Others were carried along in close association with epithelial cells, both from the superficial layer and from the glands.

It would appear that destruction of the epithelium does not occur to any extent, and that the bleeding is not severe. This would seem to constitute the chief difference between the proœstrous changes in *Tarsius*, and the corresponding changes in monkeys.

The periodicity of the sexual phenomena in *Tarsius spectrum* has already been referred to.

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[1] Stratz, *Der geschlechtsreife Säugethiereierstock*, Haag, 1898.

[2] Van Herwerden, *loc. cit.*

THE CYCLE IN INSECTIVORES

The changes which occur in the internal generative organs during the cycle in *Tupaia javanica*, and in the aberrant Insectivore, *Galeopithecus volans*, have received some slight attention.

Stratz[1] has described the existence of a blood-clot and a "menstrual" flow in *Tupaia*, and records the presence of desquamated epithelial cells in the blood-clot. Van Herwerden,[2] however, states that the individuals which Stratz examined were in the puerperal stage, and that, although *Tupaia* can experience "heat" and become pregnant at this time, trustworthy conclusions regarding the severity of the proœstrous changes cannot be drawn from such specimens. That there was considerable bleeding van Herwerden admits. Nothing is known about the periodicity of the changes in *Tupaia*.

In *Galeopithecus* van Herwerden describes uterine hyperæmia during the proœstrum. In the superficial mucosa numerous highly congested capillaries were noticed. In the later stages blood was found extravasated in the stroma, some of it being collected in spaces which were probably comparable to the sub-epithelial hæmatomata described by Gebhard in the menstruating human female. In the superficial epithelium spots were detected where a few of the cells had been removed. Bleeding did not appear to be localised to any particular area in the uterus.

Van Herwerden is certain that the changes observed could not be ascribed to a puerperal condition, as in the case of *Tupaia*, but must have been the result of a normal proœstrum. The periodicity of the changes is unknown.

THE CYCLE IN CARNIVORES

The histological changes in the non-pregnant uterus have been studied in the dog[3] and in the ferret.[4] The periods into which the uterine cycle is divided in the dog are as follows:—

(1) Period of rest - - - - -	Anœstrum.
(2) Period of growth and congestion -	Proœstrum.
(3) Period of destruction - - -	
(4) Period of recuperation - - -	Œstrus.
Followed by further growth and glandular development, these changes being succeeded by degenerative changes.	Followed by pregnancy or pseudo-pregnancy (or, as sometimes in the ferret, by metœstrum).

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[1] Stratz, *loc. cit.*

[2] Van Herwerden, *loc. cit.*

[3] Marshall and Jolly, "Contributions to the Physiology of Mammalian Reproduction: Part I. The Œstrous Cycle in the Dog," *Phil. Trans.*, B., vol. cxcviii., 1905. Marshall and Halnan, *loc. cit.*

[4] Marshall, "The Œstrous Cycle in the Common Ferret," *Quar. Jour. Micr. Science*, vol. xlviii., 1904.

It is seen that œstrus, or the time of desire, begins normally about the close of the period of destruction. With the ferret it may be very prolonged, extending until the end of the recuperation period, or even considerably beyond it. Consequently there may be no metœstrum (strictly speaking) with the ferret, since the period during which copulation can occur is liable to persist until the uterus has reached the resting stage.

(1) *Period of Rest.*—The uterine mucosa in both the dog and the ferret is bounded at the surface by an epithelium consisting of a single row of columnar or cubical cells, and is continuous with that of the glands and crypts. The latter are pits in the mucous membrane. The stroma is a connective tissue, containing numerous fusiform cells. Blood-vessels of small size are fairly common. Leucocytes do not appear to occur in the mucosa outside of the vessels. Pigment is not present at this stage, at least ordinarily.

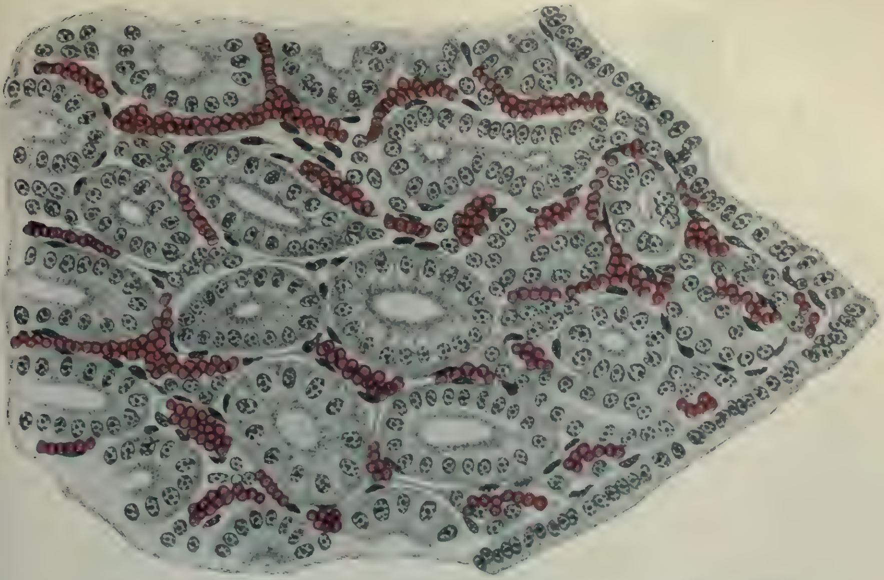

Fig. 13.—Section through proœstrous uterine mucosa of dog, showing congested vessels between the glands. (From Marshall and Jolly.)

(2) *Period of Growth and Congestion.*—The mucosa at this period becomes slightly thickened, and tends to be more compact. This is effected by cell divisions, but mitoses have not been observed. Retterer,[1] who has contributed a short account of the changes in

[1] Retterer, "Sur les Modifications de la Muqueuse Utérine à l'Epoque du Rut," *C. R. de la Soc. de Biol.*, vol. iv., 1892.

the bitch's uterus, describes the mucosa as growing to three or four times its normal thickness, but this observation has not been confirmed. The growth is accompanied by enlargement and congestion of the capillaries, which at the same time become more numerous.[1] The vessels in the surrounding muscular tissue also tend to enlarge. The epithelium undergoes no material change so far as seen. In the case of the ferret the uterine cavity is described as becoming markedly reduced in size, while the glands are stated to undergo an appreciable swelling accompanied by an increased secretory activity.

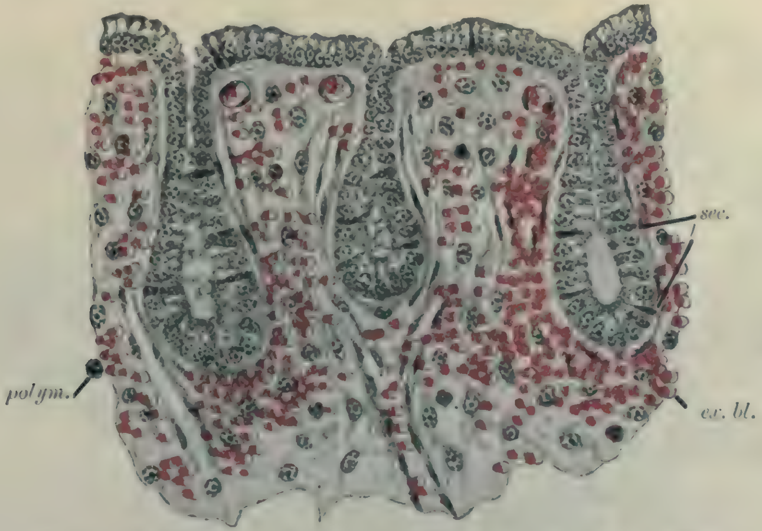

FIG. 14.—Section through procestrous uterine mucosa of dog. (From Marshall and Jolly.)

ex. bl., Extravasated blood corpuscles; *polym.*, polymorph; *sec.*, cells probably indicating secretory activity.

(3) *Period of Destruction.*—The walls of the stretched blood-vessels break down, and red corpuscles, accompanied by leucocytes, become extravasated throughout the stroma. Some of the vessels, however, remain intact. The breaking down of vessels appears to occur fairly uniformly throughout the stroma instead of being restricted to any particular portion. The extravasated blood for the most part collects immediately below the superficial epithelium, but it is not aggregated in large lacuna-like spaces, such as Heape has described in the monkey.

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[1] *Cf.* Retterer, *loc. cit.*; also Keiffer, "La Formation Glandulaire de l'Uterus," *Annales de la Soc. Medico-Chirurg. de Brabant*, 1899; and Bonnet, "Beiträge zur Embryologie des Hundes," *Anat. Hefte*, vol. xx., 1902.

These "sub-epithelial hæmatomata" have been noticed especially in the procœstrous bitch. The walls of the vessels in the muscular layers do not give way.

Eventually the extravasated blood corpuscles (or, at any rate, the majority of them) make their way into the cavity of the uterus, and thence to the vagina, where external bleeding is observed. This is especially noticeable in the case of the bitch, with which, as already mentioned, external bleeding may last for as long as ten days. The bleeding is accompanied by an increase in the mucous secretion. At about the same stage goblet-shaped cells are frequently observable in the glandular epithelium, and it is suggested that these are in some way connected with the secretory activity of the glands.

It is probable that destruction of the superficial epithelium occurs normally to a greater or less extent both in the bitch and in the ferret. Epithelial cells have been observed lying free in the uterine cavity, while, in some sections, places have been noticed where the stroma presented a raw edge, having been stripped of its epithelial covering. In the bitch a layer of flattened stroma cells may sometimes be seen in close attachment to the epithelium during the process of denudation. In the ferret it would appear that the destruction may occasionally be severer, but it is thought that this is exceptional. It has been pointed out, however, that a comparison between the thickness of the uterine wall (and conversely the size of the uterine cavity) in ferrets killed at the commencement of the recuperation period and during the period of rest, is very suggestive of a definite removal of stroma as well as of epithelium in the process of destruction.

Polymorph leucocytes have been observed in abundance at this stage in the bitch's uterus, both in the stroma and also in the cavity, and large mononuclear leucocytes (hyaline corpuscles), containing pigment derived doubtless from the extravasated blood, have also been seen to occur. Large cells, with faintly staining nuclei of very considerable size and conspicuous nucleoli, have been noticed at rare intervals lying in spaces in the stroma tissue of the procœstrous bitch. The origin and significance of these cells are not known.

There is no blood-clot formed in the uterus, either in the bitch or in the ferret.

(4) *Period of Recuperation.*—The new epithelium in the bitch is first seen as a layer of flattened cells which bear a resemblance to the cells of the stroma. Its manner of formation is an open question, but it would seem probable that it is derived mainly, if not entirely, from the remaining cells of the old epithelium, or from those of the glands. It is just possible, however, that in certain places the epithelium may be renewed from the underlying stroma tissue, as

is said by Heape (but not by van Herwerden) to be the case in the monkey.

During the earlier stages of recuperation a variable, and often a large, number of red blood corpuscles remain scattered in the stroma, chiefly in the part nearest the surface. At a later stage extravasated corpuscles are no longer seen in any quantity, while numerous new vessels appear to have been formed, presumably from pre-existing vessels.

Polymorphs are no longer common in the bitch's mucosa tissue, but leucocytes of other varieties are a characteristic feature. The following kinds have been observed: (1) Coarsely granular eosinophil cells, with lobed nuclei. These occur in the blood in cases of trichinosis, bronchial asthma, sarcoma, osteomalacia, skin diseases, and other affections, but are rare under ordinary conditions. (2) Basophil cells, with simple nuclei and containing coarse granules, but never any pigment. The number of granules varies, and in some of the cells is very small. These basophil cells are evidently similar to the mast cells of Ehrlich and the plasma cells of Unna. Mast cells are said to be often found in inflammatory areas, and are described as occurring in the stroma tissue of tumours in association with plasma cells, and also in the peripheral circulation in cases of

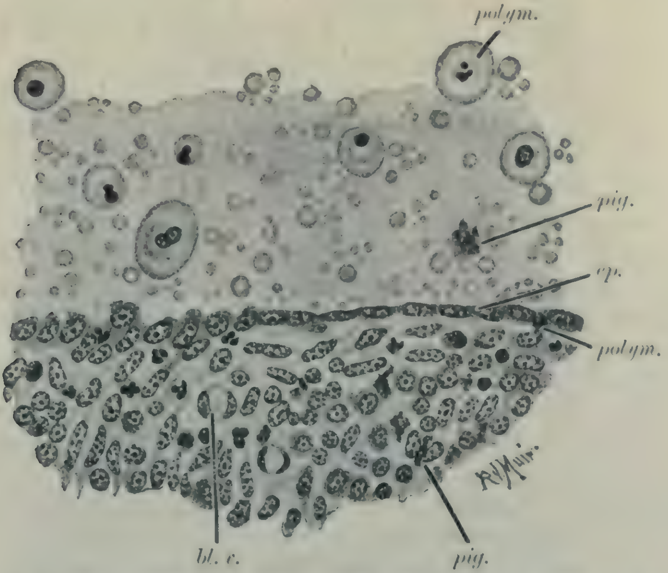

FIG. 15.—Section through edge of mucosa of dog during an early stage of recuperation. (From Marshall and Jolly.)

bl. v., Blood-vessel ; *ep.*, epithelium in process of renewal ; *pig.*, pigment ; *polym.*, polymorph.

lymphatic and myeloid leucæmia. They are especially numerous during the recuperation period of the bitch's uterus, and it is suggested that they must in some unknown way be functionally connected with that process. (3) Large mononuclear leucocytes (hyaline corpuscles or macrocytes), containing blood-pigment which gives the Prussian-blue reaction. Since pigment formation and ingestion by leucocytes are of frequent occurrence in the bitch's uterus at about this stage

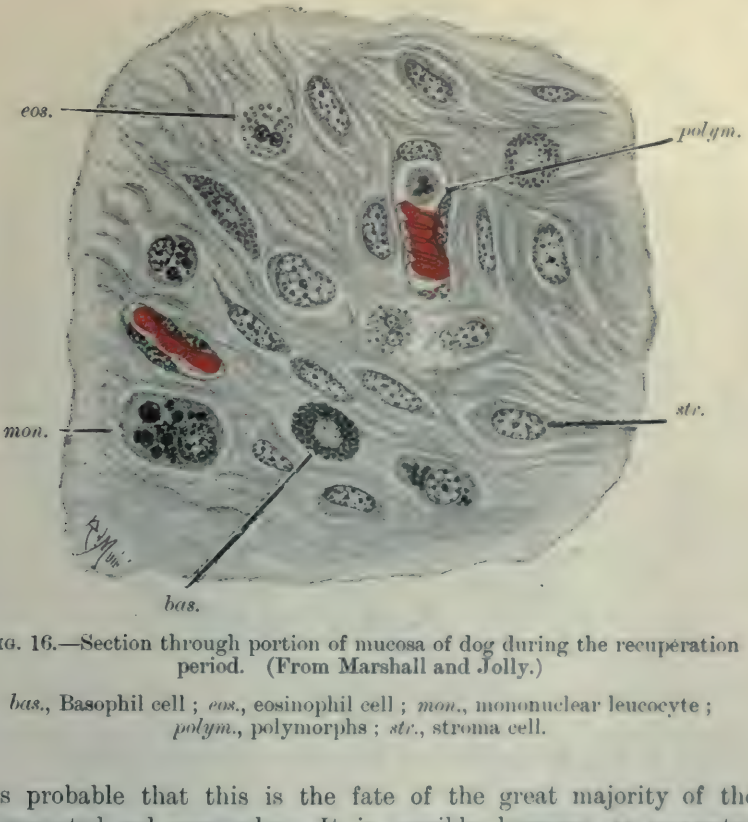

Fig. 16.—Section through portion of mucosa of dog during the recuperation period. (From Marshall and Jolly.)

bas., Basophil cell ; *eos.*, eosinophil cell ; *mon.*, mononuclear leucocyte ; *polym.*, polymorphs ; *str.*, stroma cell.

it is probable that this is the fate of the great majority of the extravasated red corpuscles. It is possible, however, as suggested in the paper from which this account is taken, that a relatively small proportion may make their way into the lymphatics, and so re-enter the circulation. Pigment formation has not been observed in the ferret.

If copulation has taken place, spermatozoa in great numbers may be observed in the deeper portions of the uterine glands, as well as along the edges of the uterine cavity.

Recuperation in the bitch is succeeded either by pregnancy or pseudo-pregnancy according to whether or not the ova discharged during œstrus are fertilised. During pseudo-pregnancy the uterus undergoes growth changes which relate chiefly to the blood-vessels and glands of the mucosa.[1] These increase in size, the whole organ assuming a histological appearance of great activity. Three weeks after the beginning of prooestrous bleeding, the epithelial cells lining the crypts and glands are columnar, and this condition remains until about the end of the fifth week when the cells become cubical. The lumina of the glands contain a colloidal secretion and in the later stages remains of desquamated epithelial cells. About the eighth or ninth week from the beginning of "heat" the capillaries begin to break down and corpuscles are freely extravasated in the

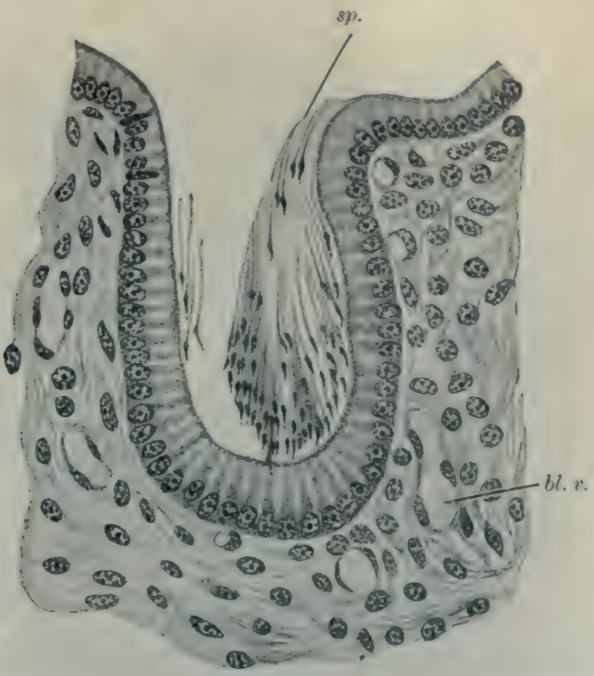

Fig. 17.—Section through mucosa of dog during a late stage of recuperation. (From Marshall and Jolly.)

bl. v., Blood-vessel ; *sp.*, spermatozoa in cavity of gland.

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[1] Marshall and Halnan, "On the Post-Œstrous Changes occurring in the Generative Organs and Mammary Glands of the Non-Pregnant Dog," *Proc. Roy. Soc.*, B., vol. lxxxix., 1917. *Cf.* Keller, "Über den Bau des Endometriums beim Hunde," *Anat. Hefte*, vol. cxviii., 1909 ; and Drahn, "Die anatomischen Veränderungen am Geschlechtsapparat unserer Haustiere bei der Brunst mit besonderer Berücksichtigung der Hündin," *Inaug.-Diss. zu Hannover*, Berlin, 1913. This memoir contains interesting comparative data.

stroma, but apart from this circumstance the mucosa shows no resemblance to that of the prœstrous stage, for the gland epithelium is either broken down or else new and attenuated instead of being columnar like that of the bitch during "heat." The complete series of changes occurring in the pseudo-pregnant uterus are in a general way similar to those occurring in the pregnant condition. In the latter the secretion coming from the glands is a source of nutriment to the fœtus (see p. 444). Decidual cells (pp. 453-5-7) are not normally found in any of the Carnivora. The degenerative changes which occur at the close of pseudo-pregnancy are perhaps comparable to those taking place in the uterus in association with parturition. The entire sequence of uterine changes are correlated with the contemporaneous series of ovarian changes, as pointed out below,

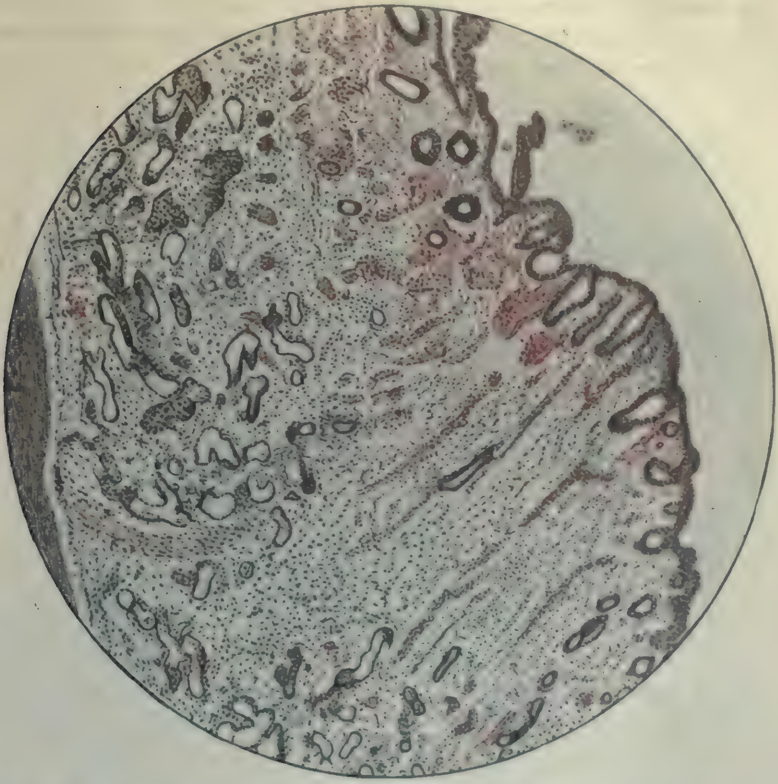

Fig. 18.—Section through uterine mucosa of bitch forty-eight days after the end of prœstrum (retrogressive stage of pseudo-pregnancy). Many of the glands are degenerating; their lumina contain colloid and the remains of desquamated epithelial cells. Extravasated blood is seen in the stroma. (From Marshall and Halnan.)

more especially in dealing with the development and retrogression of the corpus luteum (p. 373). The mammary changes are also correlated (p. 617).

THE CYCLE IN RODENTS

Considerable attention has recently been paid to the uterine changes in Rodents. In the rabbit it had long ago been noticed that the uterus is swollen and congested during "heat," and the same observation was made in the marmot (*Spermophilus citillus*).[1] Lataste[2] described proœstrous growth and congestion in the uterus of several Muridæ, and this was stated to be followed by a sanguineous discharge from the vaginal opening. Lataste also described desquamation of the uterine epithelium, but he appears to have regarded this process as taking place independently of "heat."

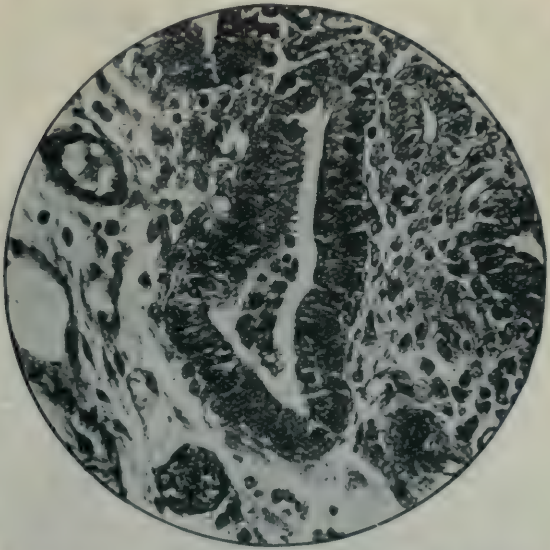

FIG. 19.—Section through portion of proœstrous uterine mucosa of rabbit, showing glandular activity, with leucocytes inside gland and passing through gland epithelium. (From Blair Bell, in *Proc. Roy. Soc. Med.*)

More recently Königstein[3] has recorded cyclical changes in several Rodents (rat, guinea-pig, etc.), and has described prooestrous desquamation of the uterine epithelium, followed by recuperation. The degenerative changes are accompanied by a secretion of mucus, and there is a marked leucocytosis over the entire generative tract. Desquamation of epithelium also occurs in the vagina. Furthermore, emigration of leucocytes between the epithelium of the glands, accompanied by great glandular activity, has been observed by Blair Bell[1] in the prooestrous uterus of the rabbit.

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[1] Rejsek, "Anheftung (Implantation) des Säugethieres an die Uteruswand, insbesondere des Eies von *Spermophilus citillus*," *Arch. f. Mikr. Anat.*, vol. lxiii., 1904.

[2] Lataste, *Recherches de Zoéthique sur les Mammifères de l'ordre des Rongeurs*, Bordeaux, 1887.

[3] Königstein, "Die Veränderungen der Genitalschleimhaut während der Gravidität und Brunst bei einigen Nagern," *Pflüger's Arch.*, vol. cxix., 1907.

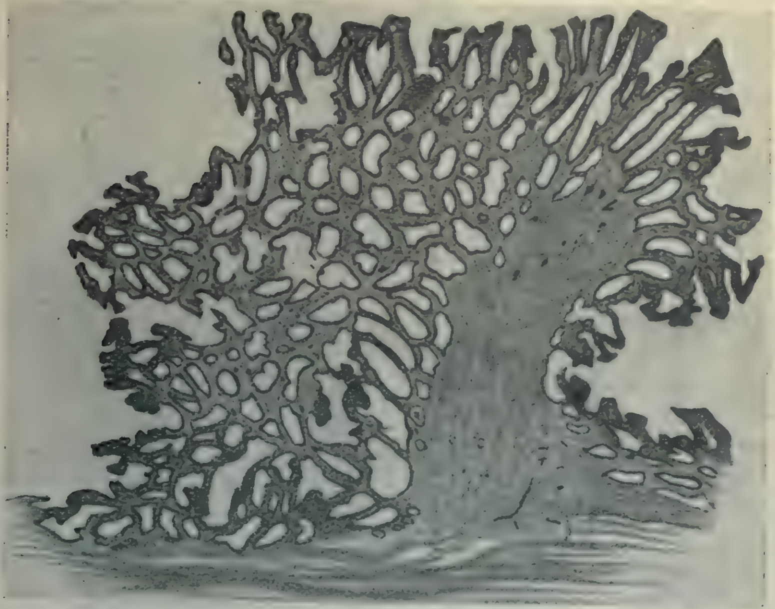

Fig. 20.—Section through uterine mucosa of rabbit nine days after sterile coition. The condition is one of pseudo-pregnancy, the glands being very well developed. (From Hammond and Marshall.)

In the rabbit pseudo-pregnant uterine hypertrophy only occurs usually under experimental conditions,[2] as when the doe has copulated with a buck in which the operation of vasectomy (or severance of the vasa deferentia) has been performed so that spermatozoa cannot be ejaculated, or where the female has had the Fallopian tubes severed. Under such conditions the corpus luteum (see p. 149) is formed in the ovary. The uterus undergoes growth, vascularisation and extensive glandular development followed by degenerative changes comparable to what occur normally in the pseudo-pregnant bitch (p. 98). The mammary glands also develop (p. 617) and secrete milk. The entire pseudo-pregnant period is somewhat less in duration than true pregnancy, which in the rabbit lasts thirty days. Exceptionally (as when two doe rabbits "jump" one another and show sexual excitement), ovulation followed by pseudo-pregnancy may take place without coition having occurred.[1]

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[1] Blair Bell, *loc. cit.*

[2] Ancel and Bouin, "Sur les Fonctions du Corps Jaune Gestatif," *Jour. Physiol. et Path. Gén.*, vols. xii. and xiii., 1910 and 1911. Hammond and Marshall, "The Functional Correlation between the Ovaries, Uterus, and Mammary Glands in the Rabbit," *Proc. Roy. Soc.*, B., vol. lxxxvii., 1914.

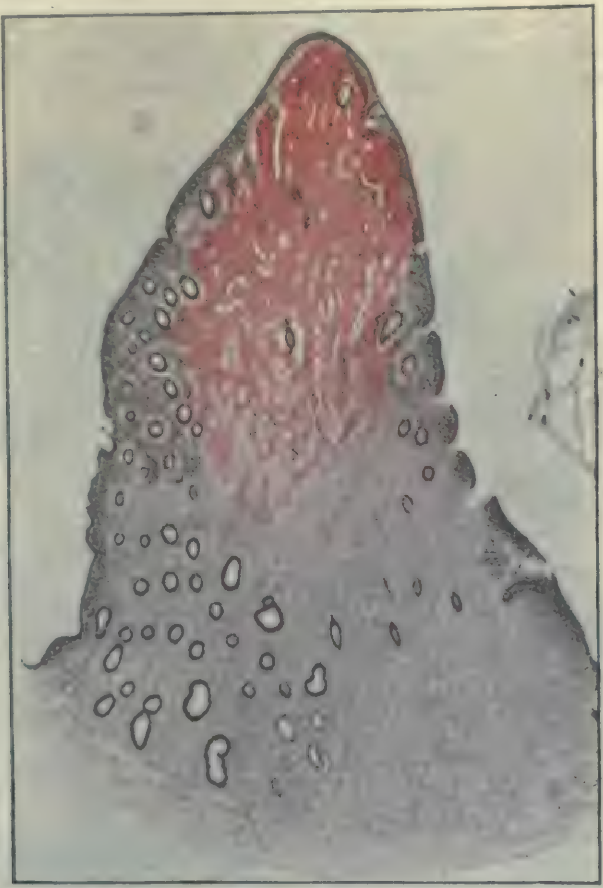

FIG. 21.—Section through uterine mucosa of rabbit twenty-four days after sterile coition (retrogressive stage in pseudo-pregnancy). A great quantity of extravasated blood is seen. The glands are still somewhat enlarged. (From Hammond and Marshall.)

In the guinea-pig Stockard and Papanicolaou[2] have described a marked correlation between the cyclical uterine changes and the developmental cycle in the corpora lutea of the ovaries (see p. 38). During the second week after a heat period the cells of the uterine and also the vaginal mucous membrane begin to show signs of degeneration and the process of desquamation commences. At the completion of two weeks the mucosa undergoes "wholesale destruction," but it is not clear whether this is to be regarded as procœstrous or pseudo-pregnant degeneration, or whether it is a case of the two processes being compressed into one such as may possibly occur in man.[1]

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[1] Hammond and Marshall, *loc. cit.*

[2] Stockard and Papanicolaou, "The Existence of a Typical Œstrous Cycle in the Guinea-Pig," *Amer. Jour. of Anat.*, vol. xxii., 1917.

Cyclical changes in the sexual organs of the rat have also been described by Long and Evans,[2] and by Kirkham and Burr.[3]

THE CYCLE IN UNGULATES

The uterine changes have been worked out in the sheep and in the sow. As described in the former[4] they relate chiefly to the blood-vessels, and are grouped according to four periods as in the case of the monkey, the dog, and the ferret, referred to above.

(1) *Period of Rest.*—The histological characters of the uterus during this period are those of an organ in a state of quiescence. Protoplasmic processes can be seen passing from certain of the stroma nuclei, but these, though denser in some places than in others, show little evidence of division. Dark brown or black pigment may be present in considerable quantities, especially in the region subjacent to the epithelium, both in the cotyledonary papillæ and (more frequently) between them and round their bases. Such pigment has not been observed in yearling sheep (*i.e.* in sheep less than a year old); neither does it appear to occur, as a rule, during the anœstrum, but only during the diœstrous interval.

(2) *Period of Growth.*—The nuclei in the stroma multiply, and the mucosa increases slightly in thickness. The epithelium, however, appears to remain unaffected. The blood-vessels increase both in

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[1] Cyclical changes in the guinea-pig, more particularly in the ovary, were previously described by Leo Loeb ("The Cyclic Changes in the Ovary of the Guinea-Pig," *Jour. of Morph.*, vol. xxii., 1911). See also Ishii ("Observations on the Sexual Cycle of the Guinea-Pig," *Biol. Bull.*, vol. xxxviii., 1920).

[2] Long and Evans, "The Œstrous Cycle in the Rat," *Anat. Record*, vol. xviii., 1920.

[3] Kirkham and Burr, "The Breeding Habits, Maturation of Eggs, and Ovulation of the Albino Rat," *Amer. Jour. of Anat.*, vol. xv., 1913. For other work on the œstrous cycle and sexual periodicity, etc., in Rodents, see abstracts of papers by Long and Evans as well as of papers by Freyer, Sutter, and others in *Proc. Amer. Assoc. Anat.*, 1920 and 1921, *Anat. Record*, vols. xviii. and xxi. Long and Evans have described pseudo-pregnancy in the rat as a result of sterile coition and of mechanical stimulation of the cervical canal.

[4] Marshall, "The Œstrous Cycle and the Formation of the Corpus Luteum in the Sheep," *Phil. Trans.*, B., vol. cxcvi., 1903.

size and number, producing uterine congestion. These changes occur both in the cotyledonary papillæ and in the intervening tissue around the bases of the papillæ.

(3) *Period of Destruction.*—The congestion is followed in most cases by the breaking down of some of the vessels. Very frequently the first extravasation takes place from vessels situated immediately below certain parts of the stroma where the nuclei are most thickly distributed. Leucocytes are extravasated along with the red corpuscles, but there is no evidence of the existence of wandering cells apart from those which are derived apparently from the broken-down vessels. The blood tends to collect below the epithelium. Bleeding into the uterine cavity may occur, but is not invariable. A few epithelial cells are sometimes torn off (presumably in places where blood is poured out into the cavity), but destruction even to this extent does not necessarily take place. Denudation of the stroma has never been observed. It would seem that the severity of the prœstrous process tends to diminish with each successive diœstrous cycle in the breeding season, and that sometimes in a late prœstrum the period of destruction is never reached, the congested vessels subsiding without undergoing rupture. Bleeding, when it does occur, appears to be more frequent in the cotyledonary papillæ than between them, and is commoner in the large papillæ than in the smaller ones.

Kazzander[1] appears to have been the first to detect extravasated blood in the sheep's mucosa. Subsequently Bonnet[2] has noted uterine bleeding in various Ruminants, as well as in the mare and sow, and Kolster[3] has made similar observations (*cf.* also Emrys-Roberts, see p. 43). Ewart also has described prœstrous extravasation and the presence of hæmatoidin crystals in the uterus of the mare. Glandular activity during heat was also noted.[4]

(4) *Period of Recuperation.*—The sheep's prœstrum may be said to end with the period of destruction, the entire process probably lasting for not longer than one or two days, its exact duration depending upon its severity. Œstrus itself, which occurs during the beginning of the period of recuperation, sometimes occupies only a few hours.

In those places where bleeding into the cavity took place in the preceding period the epithelium is renewed, apparently from the edges of the adjoining epithelium which had not suffered destruction. In this way the re-formation of the epithelium is sufficiently accounted for, since, as already remarked, only a very inconsiderable number of cells is removed during the sheep's procœstrum.

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[1] Kazzander, "Über die Pigmentation der Uterinschleimhaut des Schafes," *Arch. f. Mikr. Anat.*, vol. xxxvi., 1890.

[2] Bonnet, article in Ellenberger's *Vergleichende Physiologie der Haussäugethiere*, vol. ii., Berlin, 1892. *Cf.* also Ellenberger's article in same volume.

[3] Kolster, "Weitere Beiträge zur Kenntniss der Embryotrophe bei Indecidunten," *Anat. Hefte*, vol. xx., 1902.

[4] Ewart, "Studies on the Development of the Horse," *Trans. Roy. Soc. Edin.*, vol. li., 1915.

Congestion of the stroma gradually diminishes, and the mucosa as a whole undergoes a slight shrinkage. It would appear that a few new capillaries are formed, but there is no evidence that any of the extravasated corpuscles are gathered up afresh into the circulatory system. On the other hand, there are ample indications that all those corpuscles which remain in the tissue become transformed into pigment, as originally concluded by Bonnet.[1] According to this investigator, the extravasation takes place in the deeper mucosa, and the derivatives of the corpuscles are carried in the form of pigment to the more superficial area by wandering cells. Kazzander,[2] however, does not admit the agency of leucocytes; but the most recent observations support Bonnet's conclusions, excepting that (as previously stated) the extravasation which takes place during the destruction period is in the superficial mucosa rather

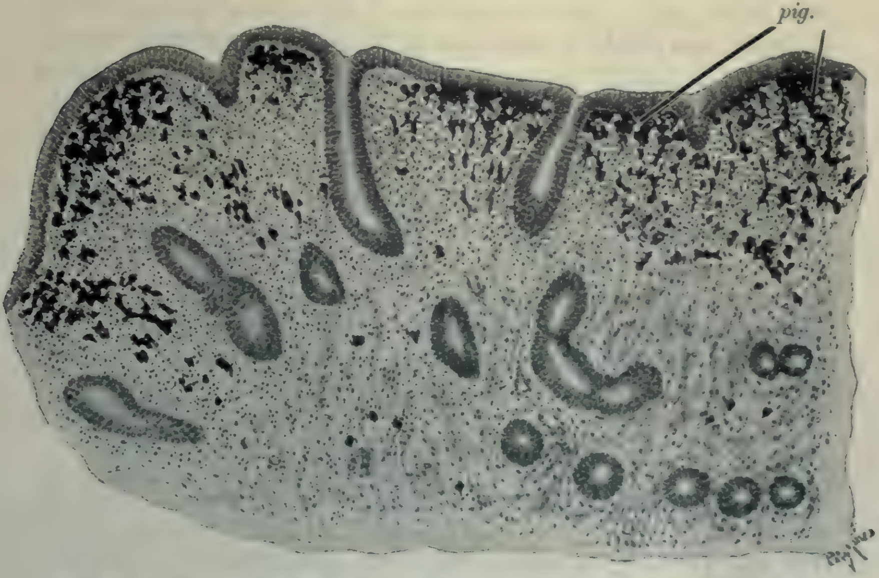

FIG. 22.—Section through portion of uterine mucosa of sheep, showing black pigment (*pig.*) formed from extravasated blood.

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[1] Bonnet, "Ueber Melanose der Uterinschleimhaut, etc.," *Deutsche Zeitsch. f. Thiermedizin*, vol. v., 1880, and vol. vii., 1882; "Beiträge zum Embryologie der Wiederkauer, etc.," *Arch. f. Anat. u. Phys.*, Anat. Abth., 1884.

[2] Kazzander, *loc. cit.*

than in the deeper tissue. Thus, although leucocytes are probably involved in the process of pigment formation, there is no need to assume that they carry the extravasated corpuscles to the region where pigment is most abundant. Sometimes the interior of the uterus appears superficially to be perfectly black with pigment, but in such cases the pigment is, no doubt, derived from blood which had been extravasated during a series of procœstrous periods, and not merely during the most recent one. Assheton[1] states that the pigment so formed is subsequently disposed of.

Corner[2] has described cyclic changes in the uterus of the sow. Just before œstrus there is evidence of activity on the part of the epithelial cells in which mitotic figures may be found, while a contrary process is manifested here and there in nuclear chromatolysis and degenerate changes, and neutrophilic polymorph leucocytes in the sub-epithelial stroma become very numerous. During œstrus the stroma is very œdematous. The post-œstrous changes are very marked. The epithelial cells actively secrete a serous fluid from the eighth to the tenth day, after which they subside to a cuboidal form, and there is a slow reversion to the œstrous type. Post-œstrous glandular hypertrophy is not definite, but otherwise the changes are clearly suggestive of an abbreviated pseudo-pregnancy occurring under the influence of the corpus luteum of the ovary (see above, pp. 99-101, and below, pp. 371-372).

THE CYCLE IN MARSUPIALS

The changes which occur in the internal generative organs of the Marsupial cat (*Dasyurus viverrinus*) have been described fully by Hill and O'Donoghue (see p. 36). The procœstrum lasts for from four to twelve days, and during this time the uterine mucosa increases in thickness and becomes more vascular, while its glands lengthen and become convoluted and the epithelium tends to thicken. During œstrus, which lasts one or two days, the changes above described are continued. Following œstrus there is, according to these authorities, a post-œstrous period lasting five or six days and terminated by ovulation, and during which the uterine changes continue further. This is followed by either pregnancy or pseudo-pregnancy. During pseudo-pregnancy the uteri enlarge considerably and become still more vascular, and these changes are succeeded by degeneration and desquamation of epithelium with extravasation of blood. Eventually regeneration sets in and the mucous membrane undergoes recuperation. According to Hill and O'Donoghue the changes which occur during pseudo-pregnancy are comparable to those of the proœstrum in the Eutheria in which animals the cyclical events have been thrust forward to a much earlier stage as compared with the marsupial. It has been pointed out, however, that there is no necessity to take this view since the pseudo-pregnant uterine phenomena of *Dasyurus* find their parallel in the rabbit under experimental conditions, and normally in the monœstrous dog[1] (see p. 98).

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[1] Assheton, "The Morphology of the Ungulate Placenta," *Phil. Trans.*, B., vol. cxcviii., 1906. Changes in the uterine mucosa have also been described in pigs. See Steyn, *Oster. Wschr. f. Tierheilkunde*, 1912; and Geist, 1913, *loc. cit.*

[2] Corner, "Cyclic Changes in the Ovaries and Uterus of the Sow, etc." *Contributions to Embryology*, No. 64, Carnegie Institute (Washington) Publications, 1921.

A consideration of the facts set forth in this chapter should leave one in no doubt regarding the essential similarity between the menstrual cycle in the Primates, and the œstrous cycle in the lower Mammalia. Those who have denied that there is any correspondence between "heat" and menstruation[2] have laid stress upon the assertion that whereas "heat" in the lower animals is the time for coition, this act, as a general rule, is not performed during menstruation. But, as was first pointed out by Heape, it is the proœstrum alone and not the entire "heat period" (a term used generally to include both proœstrum and œstrus) which is the physiological homologue of menstruation; and, moreover, the latter process in many of the Primates is succeeded by a regular post-menstrual œstrus.

It is possible, however, that menstruation in man and monkeys represents pseudo-pregnant destruction as well as proœstrous degeneration, the complete cycle of changes being compressed into one month, and unless some such explanation be adopted one must suppose that the processes of pseudo-pregnancy are unrepresented in the menstrual cycle.

Nielsen[3] goes further and supposes that menstruation in man does not represent the proœstrum at all, but corresponds to a later phase in the cycle which must be identified with pseudo-pregnant destruction, but the preponderating evidence is against this view.

It has been shown that although the changes which occur in the uterus during the cycle present a general similarity in the various

[1] Marshall and Halnan, *loc. cit.* In all these animals there are parallel pseudo-pregnant changes in the mammary gland and in the development, persistence, and retrogression of the corpora lutea (see below, pp. 371-373).

[2] Beard, in *The Span of Gestation and the Cause of Birth* (Jena, 1897), says, "very little is required in disproof" of this correspondence.

[3] Nielsen, "Om Corpus Luteums Funktion og den Fysiologiske Korrelation mellem Ovarier og Uterus," *Den Kgl. Veterinær og Landbohøjskole Aarsskrift*, 1921. According to this author, in the cow, sow, and the bitch, ovulation seems to occur before or at the beginning of proœstrum, but see below, pp. 130-133. Compare Leo Loeb, *Surg., Gyn., and Obstet.*, vol. xxv., 1917.

mammalian types in which they have been studied, yet there is a considerable amount of variation in the severity and duration of the prooestrous phenomena. The extent of the congestion, and the destruction which usually succeeds it, are greatest, as a rule, in the highest Mammals, and comparatively slight in the Rodentia and Ungulata.

The purpose or meaning of the prooestrum, and the factors which contribute to its occurrence, will be considered as fully as the present knowledge of the subject permits, after the changes which take place in the ovaries have been dealt with, in a future chapter of this work. It may be at once stated, however, that most authorities are now agreed that the menstrual process is in some sense a preparation for the attachment of an ovum to the wall of the uterus, but opinions differ as to the precise nature of the preparation. On the other hand, it is evident that the changes involved in menstruation are not absolutely essential, since there are records of pregnancy occurring in individuals who had never experienced menstruation. Moreover, there is evidence that the prooestrous discharge may be not only of no utility to the organism, but may even become injurious, as in the more severe cases of menstruation among women.

In view of these facts it may be called in question whether the prooestrous changes in the uterus should not be regarded merely as the result of a wave of disturbance which ushers in the period of desire, and is of the nature of a consequence rather than a purpose. This is in accord with Metchnikoff's suggestion,[1] that the catamenia in women are essentially a "disharmony" of organisation, which has been brought about as the result of modifications acquired recently in the history of the species. If this is so, a similar explanation must be adopted in the case of those animals which experience an especially severe prooestrum. According to such a view as this the phenomena of menstruation must be looked upon as belonging to the borderland of pathology. In this connection the large number of leucocytes which attend the menstrual process, some of them clearly phagocytic in function, is not altogether unsuggestive.

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[1] Metchnikoff, *The Nature of Man*, Mitchell's Translation, London, 1903.

CHAPTER IV

CHANGES IN THE OVARY—OÖGENESIS—GROWTH OF FOLLICLES—OVULATION—FORMATION OF CORPORA LUTEA AND ATRETIC FOLLICLES—THE SIGNIFICANCE OF THE PROŒSTROUS CHANGES IN THE UTERUS

> "The newest freak of the Fallopian tubes and their fimbriæ, and the very latest news from the ovisac and the corpora lutea."—John Brown, *Horæ Subsecivæ.*

Development of Ovary and Oögenesis

The animal egg is a large spheroidal cell consisting of external protoplasm or cytoplasm, a nucleus or germinal vesicle, and a nucleolus or germinal spot.[1] Within the cytoplasm is a mass of food material or yolk (sometimes known as deutoplasm), the quantity of which varies slightly in different Mammalia, and is very considerable in birds and certain other animals. The unfertilised ovum differs from the male germ-cell or spermatozoön in its devoting itself mainly to the storage of food-substance and accumulation of potential

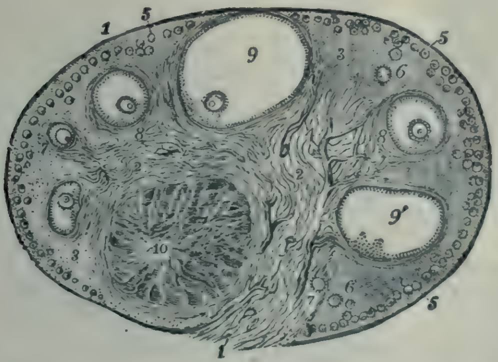

Fig. 23.—Section through ovary of cat. (Schrön.)

1, Outer surface ; 1′, attached border ; 2, fibrous central stroma ; 3, peripheral stroma ; 4, blood-vessels ; 5, young follicles ; 6, 7, 8, 9, and 9′, larger developing follicles ; 10, corpus luteum.

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[1] A centrosome has been described as present in the ova of some animals. For a detailed description of the ovum in different forms see Wilson, *The Cell in Development and Inheritance*, 2nd Edition, New York, 1900.

energy, for it is incapable of active movement. The metabolic processes of the ovum, therefore, are almost entirely constructive, while those of the spermatozoön are largely destructive. The function of the ovum is to conjugate with the spermatozoön, and subsequently, by a lengthy process of cell division, to give rise to a new individual.

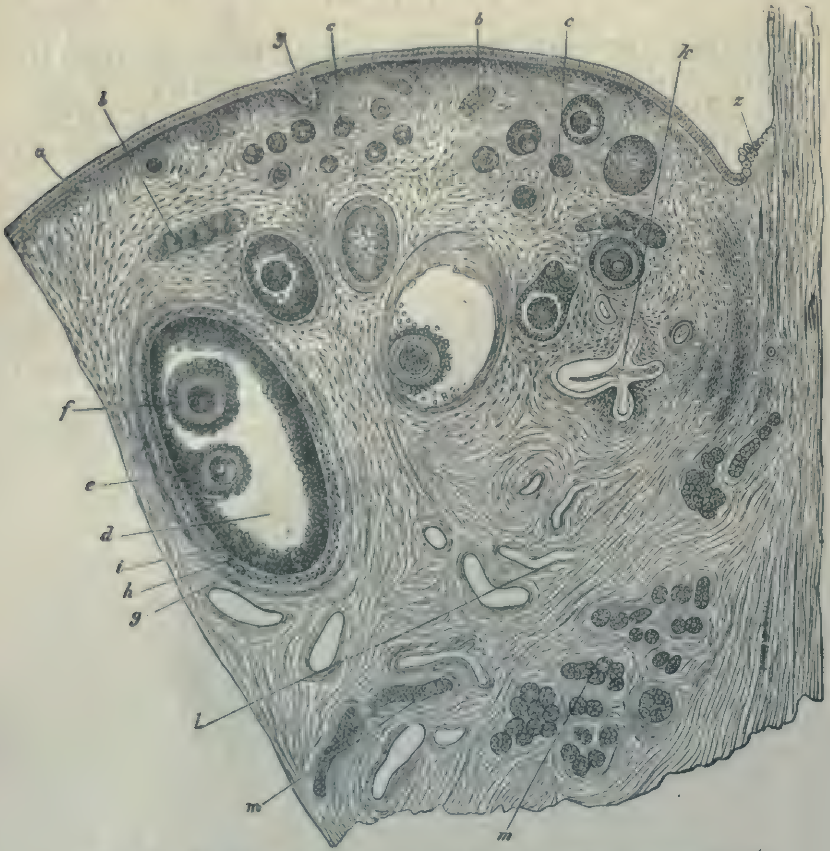

FIG. 24.—Section through ovary of adult dog. (From Waldeyer.)

a, Germinal epithelium ; *b*, remains of egg-tubes ; *c*, small follicles ; *d*, more advanced follicle ; *e*, discus proligerus and ovum ; *f*, second ovum (a rare occurrence) ; *g*, theca externa of follicle ; *h*, theca interna ; *i*, membrana granulosa ; *k*, degenerate follicle ; *l*, blood-vessels ; *m*, tubes of parovarium ; *y*, involuted germinal epithelium ; *z*, transition from germinal to peritoneal epithelium.

The mammalian ovary,[1] or organ in which the ova are produced, is composed of a stroma of fibrous connective tissue, which contains some plain muscular fibres (especially in the neighbourhood of the attachment to the broad ligament) as well as numerous blood-vessels. The surface is lined by a layer of columnar epithelial cells. Within are a number of vesicles of various sizes, each with an ovum, surrounded by an epithelium. These are called Graafian follicles. Certain other structures, consisting of very large yellow-coloured cells enclosed by a branching network of connective tissue, are also often found. These are the corpora lutea or discharged follicles to be described more fully later. The stroma contains, further, a varying number of epithelioid interstitial cells.

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[1] See also Stratz, *Der geschlechtsreife Säugethiereierstock*, Haag, 1898.

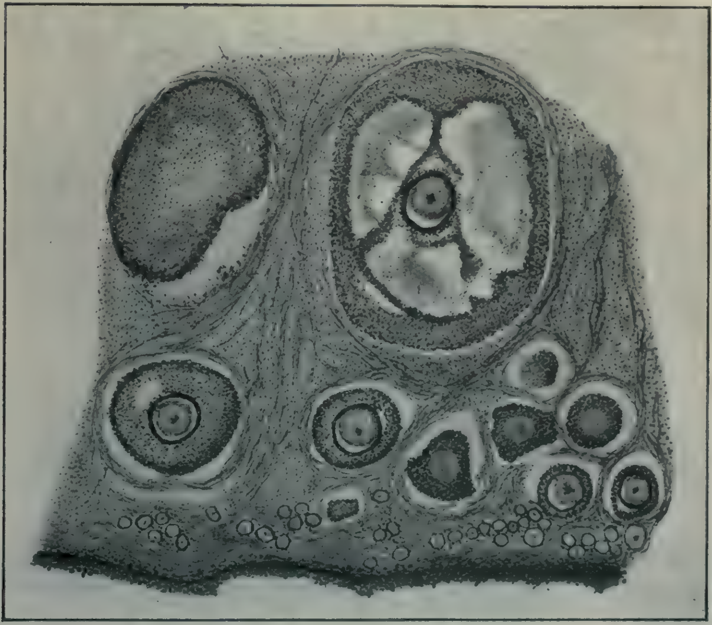

FIG. 25.—Section through ovary of rabbit, showing follicles and ova in different stages of development. (L. F. Messel.)

In order to gain a proper understanding of the structural and functional relations of the different parts of the ovary, it is necessary to make some study of its developmental history.

Pflüger[1] appears to have been the first to regard the ova[2] and epithelial cells of the Graafian follicles as originating either in the form of ingrowths simulating tubular glands, or as solid columns of cells from that embryonic layer which Waldeyer afterwards designated the germinal epithelium. The tubular ingrowths had already been noticed by Valentin,[1] who, however, failed to recognise their connection with the germinal epithelium. Later observers, however, did not confirm the tubular origin of the ovary.

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[1] Pflüger, *Ueber die Eierstöcke der Säugethiere und des Menschen*, Leipzig, 1867.

[2] The mammalian ovum was discovered by von Baer (*Ueber Entwickelungsgeschichte der Thiere—Beobachtung und Reflexion*, vol. i., Königsberg, 1828). In 1861 Gegenbaur showed that the vertebrate ovum was a single cell.

To Waldeyer belongs the credit of first recognising the true nature and significance of the process of egg formation, an account of which was published in his famous monograph, *Eierstock und Ei.*[2] He found that in the chick, on the fourth day of development, the cœlomic epithelium which covers the inner surface of the Wolffian body became differentiated from the tissue surrounding it, the cells being relatively large and cuboidal in shape. A little later he observed that the cells had multiplied to such an extent as to give rise to a distinct elevation. In this way the germinal epithelium was formed, and this marked the site of the future ovary. The mesoblast underlying the germinal epithelium is described as growing upwards among the cells of the latter, and so giving rise to the appearance of those germinal ingrowths or "egg-tubes," which were described by Pflüger.

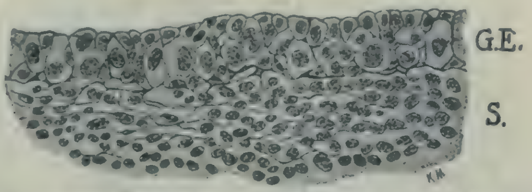

FIG. 26.—Section through ovary of pig embryo. (From Williams' *Obstetrics*, Appleton & Co.)

G.E., Germinal epithelium ; S., stroma.

The cells of the germinal epithelium are thus divided by mesoblast into clusters of "egg-nests" which contain the primordial ova, as Waldeyer has shown. As a result of this process two zones of tissue are formed in the future ovary. The outer or cortical zone consists of clusters of cells derived from the germinal epithelium, with mesoblastic processes in between them. The inner or medullary zone is composed at first entirely of mesoblast, which gives rise to the vascular tissue and stroma of the ovary.

The majority of investigators, including Balfour,[3] Schafer,[4] Nagel,[5] and von Winiwarter,[1] have followed Waldeyer in supposing that the follicular epithelial cells (which form the innermost layer of the wall of the Graafian follicle) are derived like the ova from the germinal epithelium. Schafer described appearances indicating the possibility of the innermost layer of follicular epithelium being derived from the ovum itself; but, as he himself pointed out, this view does not involve any morphological absurdity if the ova and follicle-cells have a common origin. Balfour described protoplasmic masses of embryonic ova in which the cells appeared to be united together in such a way as to suggest that one ovum might undergo development at the expense of the others. Somewhat similar appearances have been observed in the bat's ovary by van Beneden,[2] who regarded

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[1] Valentin, "Ueber die Entwickelung der Follikel in dem Eierstocke der Saugethiere," *Muller's Arch.*, 1838.

[2] Waldeyer, *Eierstock und Ei*, Leipzig, 1870.

[3] Balfour, "Structure and Development of the Vertebrate Ovary," *Quar. Jour. Micr. Science*, vol. xviii., 1878.

[4] Schafer, "On the Structure of the Immature Ovarian Ovum, etc.," *Proc. Roy. Soc.*, vol. xxx., 1880.

[5] Nagel, "Das menschliche Ei," *Arch. f. Mikr. Anat.*, vol. xxxi., 1888.

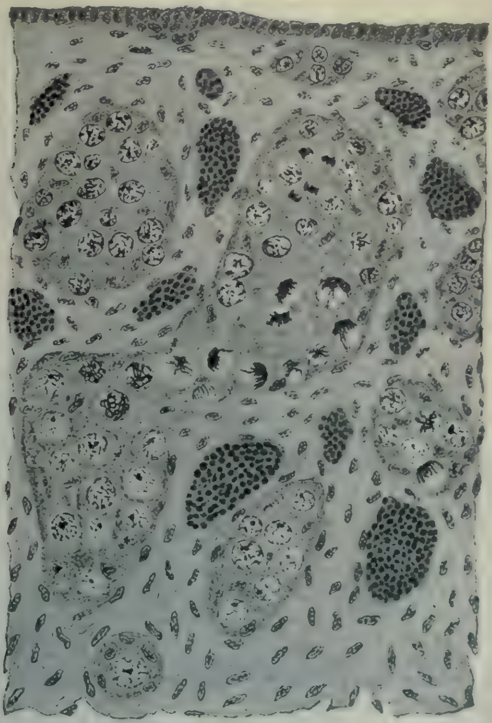

FIG. 27.—Cortex of pig embryo, showing germinal epithelium, Pflüger's tubes with ova in various stages of development. (From Williams' *Obstetrics*, Appleton & Co.)

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[1] Von Winiwarter, "Recherches sur l'Ovogenèse, etc.," *Arch. de Biol.*, vol. xvii., 1901.

[2] Van Beneden and Julin, "Observations sur la Maturation, etc.," *Arch. de Biol.*, vol. i., 1880.

them as syncitia from which both ova and follicular epithelial cells took origin.

On the other hand, Kölliker believed that the follicle-cells arose from the epithelium of the Wolffian body, while Foulis,[1] Schrön,[2] Wendeler,[3] and Clark,[4] expressing the opinion that the follicle-cells are derived from the mesoblast, have also dissented from this the more usual view. Clark, in support of his theory, has pointed out that the cells which immediately surround the primordial follicles are often spindle-shaped and similar in appearance to many of the stroma cells, and further, that the primordial ova in the early stages of development are often apparently in direct contact with connective tissue which obviously had been derived from the embryonic mesoblast.

Most authorities, however (including the more recent investigators), are of opinion that the follicular epithelial cells, in common with the ova, are derived from the germinal epithelium. Further, Miss Lane-Claypon[5] has shown that the epithelioid interstitial cells,[6] which (in addition to the connective tissue and plain muscle fibres) are contained in the ovarian stroma, in all probability arise also from the original germinal epithelium. This has been confirmed by Miss M'Ilroy,[7] who states that the primordial germ-cells or oögonia give rise, after a series of two or more divisions, to ova, follicle-cells, and interstitial cells. The two latter types of

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[1] Foulis, "The Development of the Ova, etc.," *Jour. Anat. and Phys.*, vol. xiii., 1876.

[2] Schrön, "Beitrag zur Kenntniss der Anatomie und Physiologie des Eierstocks der Säugethiere," *Zeitsch. f. wissensch. Zool.*, vol. xii., 1863.

[3] Wendeler, "Entwickelungsgeschichte und Physiologie der Eierstöcke," Martin's *Die Krankheiten des Eierstocks und Nebeneierstocks*, Leipzig, 1899.

[4] Clark, "The Origin, Growth, and Fate of the Corpus Luteum," *Johns Hopkins Hospital Reports*, vol. vii., 1898.

[5] Lane-Claypon, "On the Origin and Life History of the Interstitial Cells of the Ovary of the Rabbit," *Proc. Roy. Soc.*, B., vol. lxxvii., 1905.

[6] For a comparative account of the interstitial substance in the ovaries of various Mammals, with references to the literature, see Fraenkel, "Vergleichende Histologische Untersuchungen über das Vorkommen drüsiger Formationen im Interstitiellen Eierstocksgewebe," *Arch. f. Gynäk.*, vol. lxxv., 1906. According to Ancel and Bouin interstitial cells are not present in the ovaries of animals which ovulate spontaneously, the corpus luteum taking their place. (Bouin and Ancel, "Sur les Homologies et la Signification des Glandes à Sécrétion Interne de l'Ovaire," *C. R. Soc. Biol.*, vol. lxvii., 1919.) See also O'Donoghue ("On the Corpora Lutea and the Interstitial Tissue of the Ovary in Marsupials," *Quar. Jour. Micr. Science*, vol. lxi., 1916), and Cesa-Bianchi ("Osservazione sulla struttura e sulla funzione della cosidetto glandiola interstiziale dell' ovaia," *Arch. d. Fis.*, vol. iv., 1907). The latter author says that there is an inverse relation between the size of the corpus luteum and the development of the interstitial cells in the various species of Mammals; also that in hibernating animals the interstitial cells are poorly developed during the winter sleep, but during summer and particularly at the time of sexual activity they are very numerous. (See p. 331.) See also Athias, "Recherches sur les Cellules Interstitielles de l'Ovarie des Cheiroptères," *Arch. de Biol.*, vol. xxx., 1919; and Rasmussen, "Cyclic Changes in the Interstitial Cells, etc.," *Endocrinology*, vol. ii., 1918. See also footnote, p. 120.

[7] M'Ilroy, "The Development of the Germ-Cells in the Mammalian Ovary," *Proc. Roy. Soc. Edin.*, vol. xxxi., 1910.

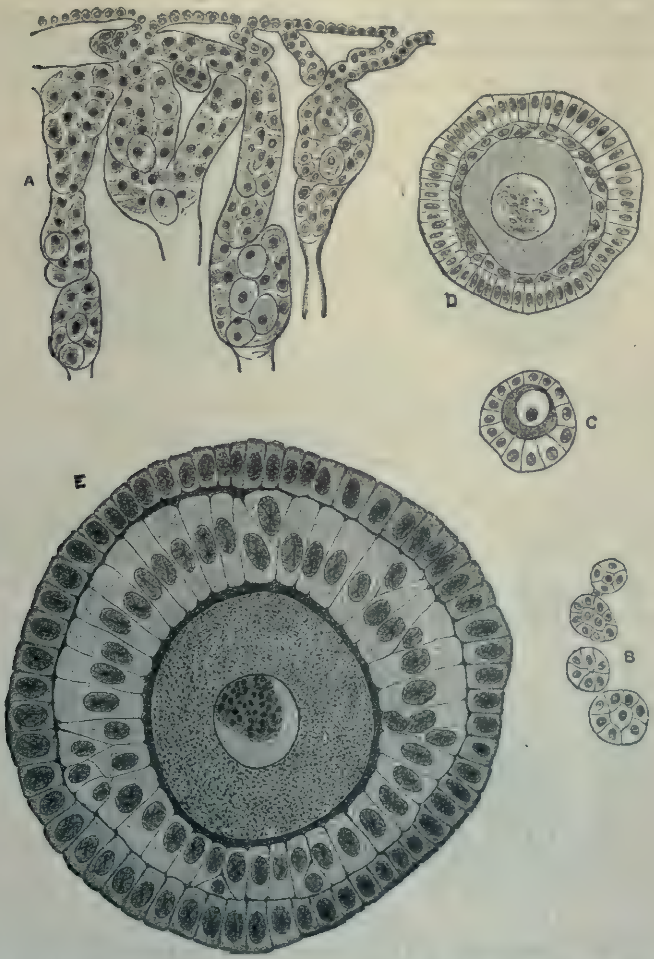

Fig. 28.—Various stages in the development of the Graafian follicle of the rabbit. (From Schafer.)

A, From young rabbit, showing Pflüger's egg-tubes; B, C, D, E, successive later stages.

cell may remain for a time as reserve cells or may be absorbed as pabulum for the developing cocyte.

The changes involved in the production of ova have been fully investigated by von Winiwarter[1] in the rabbit. These changes which chiefly concern the chromatin of the nucleus may be summarised as follows:—

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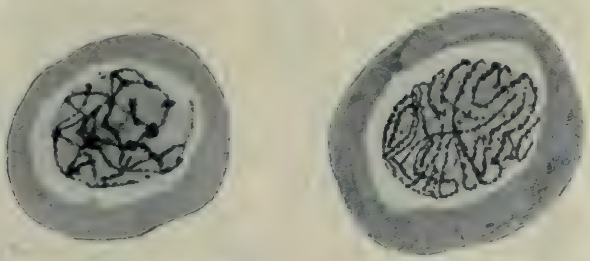
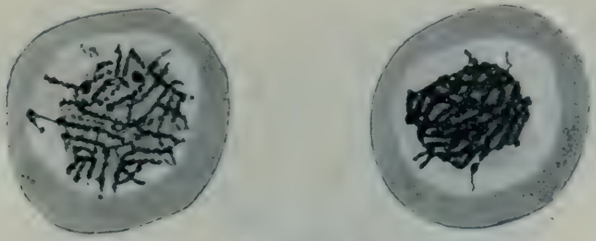
[1] Von Winiwarter, "Recherches sur l'Ovogenèse de l'Organogenèse de l'Ovaire des Mammifères," *Arch. de Biol.*, vol. xvii., 1900.

I. Early changes: (*a*) Protobroque cells, Variety *a*.—The nuclei are granular in appearance, the chromatin is arranged irregularly, and there is no reticulum. These are the original germinal epithelial nuclei. (*b*) Protobroque cells, Variety *b*.—The cells belonging to variety *a* divide, and give rise to more cells of the same kind, as well as to protobroque cells of the *b* variety. In the latter the nuclei are less granular, and contain a certain number of fine chromatin filaments. (*c*) Deutobroque cells.—The protobroque cells of the *b* variety likewise divide, and give rise to more protobroque cells, similar to themselves and also to deutobroque cells. These latter are larger in size, and contain nuclei with the chromatin arranged in the form of a reticulum.



Early ovogenetic stage. Leptotenic stage.

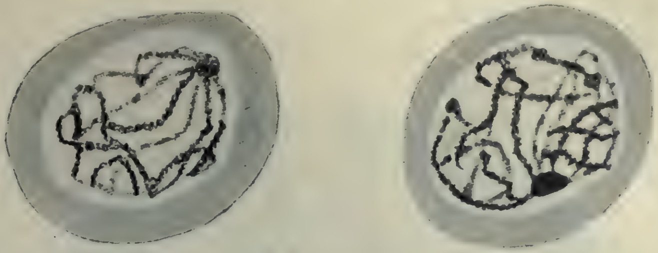
FIG. 29.—Developing ova from ovary two days before birth. (After Lane-Claypon.)



Early. Synaptenic stage. *Late.*

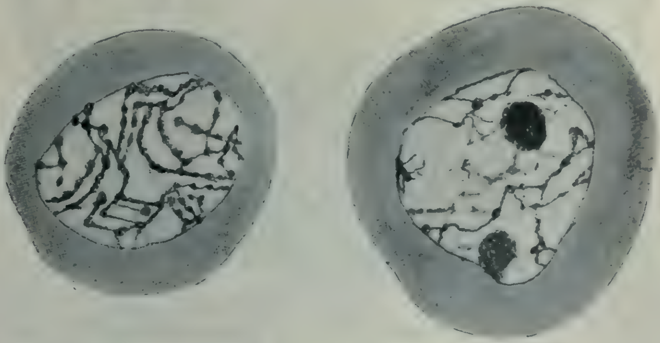
FIG. 30.—Developing ova from ovary about one day before birth. (After Lane-Claypon.)

II. Later changes: (*a*) Leptotenic stage.—Certain of the deutobroque nuclei become gradually differentiated, the chromatin during the leptotenic stage passing through a process in which it breaks up into fine filaments; these are distributed over the nuclear region. (*b*) Synaptenic stage.—The filaments become congregated together in the form of a lump, or dark mass, heaped up at one side of the nuclear region. (*c*) Pachytenic stage.—The nuclear filaments again become unwound, and spread themselves out over the whole nuclear region; they are, however, considerably coarser than in the earlier stages. (*d*) Diplotenic stage.—The chromatin strands split along their whole length, and the two halves of each strand at first lie in pairs near to one another. (*e*) Dictyate stage.—The split strands pass away from one another, and the chromatin generally becomes distributed once more throughout the nuclear region in the form of a reticulum.



Pachytenic stage.

FIG. 31.—Developing ova from ovary one day after birth. (After Lane-Claypon.)



Diplotenic nucleus three days after birth.

Dictyate nucleus seven days after birth.

FIG. 32.—Developing ova. (After Lane-Claypon.)

The nucleus or germinal vesicle of the primordial ovum thus produced then enters upon a long period of rest, the changes involved in oögenesis having been completed.[1]

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[1] For an account of the minute structure of the Mammalian egg, together with a résumé of the literature, see van der Stricht, "La Structure de l'Œuf des Mammifères," Part I., *Arch. de Biol.*, vol. xxi., 1904; Part II., *Bull. de l'Acad. Royale de Médecine de Belgique*, Bruxelles, 1905; Part III., Bruxelles,

Some of the deutobroque cells, instead of passing through the transformations above described, rest for a time and subsequently undergo retrogressive changes, becoming converted, according to Miss Lane-Claypon, either into follicular epithelial cells or into interstitial cells. "Every cell of the germinal epithelium is probably a potential ovum, relatively very few remaining in the protobroque state, although some may still be seen at the periphery in ovaries of the eighteenth day [of gestation in the rabbit]. Incomparably the greater part pass into the deutobroque state, preparatory, doubtless, to the formation of ova. All cannot become ova, for the other forms of cell are necessary for the maintenance of the ovarian functions; possibly, therefore, only the most robust cells, and those which are most conveniently situated for obtaining nourishment, undergo the ovogenetic changes. This suggestion would seem to be borne out by the fact that many more of the central cells, which are nearer the

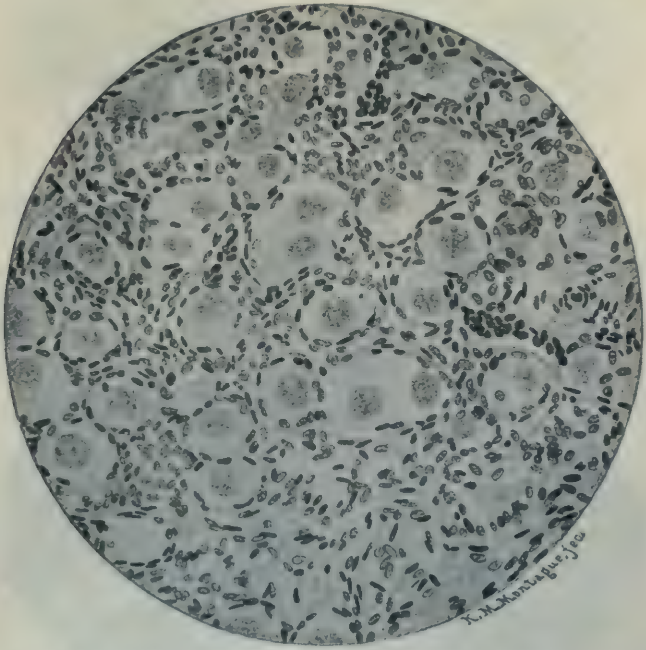

Fig. 33.—Ovary at birth, showing primordial follicles. ×300. (From Williams' *Obstetrics*, Appleton & Co.)

1909. For a general account of the egg and the phenomena of oögenesis in the different groups of animals, both Vertebrate and Invertebrate, with a complete bibliography, see Waldeyer, "Die Geschlechtszellen," in Hertwig's *Handbuch der Entwicklungslehre der Wirbeltiere*, vol. i., Jena, 1903; also Wilson, *The Cell in Development and Inheritance*, 2nd Edition, New York, 1900.

food supply, undergo ovogenesis than of the peripheral ones. The rest of the cells, which are not able, for one cause or another, to undergo these changes, appear to remain quiescent for a while, until finally they regress, and pass into a condition of subserviency to the needs of those which have become ova. Both follicle-cells and interstitial cells are, however, still potential ova. They have passed through the initial stages, and only need enlargement and nuclear transformations in order to become ova should the appropriate stimulus be given [as will be described below, p. 155]. This chance is not given to the follicle-cells. As soon as the follicles begin to grow they multiply rapidly, and probably provide, by their [partial] disintegration, the follicular secretion upon which the ovum feeds and grows."[1]

The description given above of the origin of the follicle and interstitial cells applies especially to the rabbit. Miss Lane-Claypon has also investigated their developmental history in the rat,[2] and expresses belief that in this animal also they are derived from the germinal epithelium by a similar process of differentiation. Both follicular epithelial cells and interstitial cells are stated to pass through identically the same stages, but the latter are said to remain grouped together in the spaces between the follicles instead of arranging themselves around the diplotenic nuclei of the developing ova.

Thus it appears that the ova, the follicular epithelial cells, and most probably also the interstitial cells, are all derived from the germinal epithelium by processes involving changes in the nuclear chromatin; but that, whereas these changes are similar in the case of the follicle and interstitial cells, those undergone by the developing ova are more extensive and show a greater complexity.

The significance of the common origin of these different ovarian elements will be more apparent when we consider the views which are held regarding the further development and the probable functional importance of these cells.

It should be mentioned, however, that Allen[3] and Sainmont,[4] working on the organogenesis of the ovary in the rabbit and the cat respectively, have come to the conclusion that the ovarian interstitial cells have a connective tissue origin, but these investigators do not appear to have traced the successive stages of cellular development with the same completeness as Miss Lane-Claypon.[1] Sainmont is of opinion that they have a trophic function, a suggestion which was first made by Pflüger.[2]

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[1] Lane-Claypon, *loc. cit.*

[2] Lane-Claypon, "On Ovogenesis and the Formation of the Interstitial Cells of the Ovary," *Jour. Obstet. and Gynæc.*, vol. xi., 1907.

[3] Allen, "The Embryonic Development of the Ovary and Testis of the Mammals," *Amer. Jour. of Anat.*, vol. iii., 1904. Allen describes the interstitial cells in a three-months-old rabbit as being derived from certain cells in the thecæ internæ of degenerate follicles. The cells are said to lose their walls, become irregular in shape, and undergo a rapid process of amitotic division, after which they become transformed into typical interstitial cells.

[4] Sainmont, "Recherches relatives à l'organogenèse du Testicule et l'Ovaire chez le Chat," *Arch. de Biol.*, vol. xxii., 1905.

There would seem to be no doubt that the developing ova in the immature ovary subsist and grow at the expense of the surrounding tissue. Thus protoplasmic masses, formed by the aggregation of very young ova, have been described by Balfour,[3] who made the suggestion that one ovum may develop at the cost of the others. These aggregations of ova were noticed in the ovary of the fœtal rabbit at about the sixteenth day of pregnancy. A day or two previously the ova were observed to be separate. Miss Lane-Claypon, who confirms the observation, is of opinion that Balfour's suggestion was right, and that the ova which disappear serve ultimately as food-stuff for the one ovum whose condition happens to be the most vigorous. "This cannibalism on the part of the young ovum is not surprising, if the life of an ovum be considered. It is really but the normal condition of the cell at all its stages of development; it grows and fattens at the expense of other cells. In the young ovary, it is starting its first stage of growth and must devour other cells; later on, during the growth of the follicle, it lives upon the follicle-cells, and later still, when, after fertilisation, the [term] ovum in its extended sense refers to the young fœtus, [this latter] lives on the material provided by the cells of the maternal organism."[4]

Maturation and Ovulation

The youngest and smallest Graafian follicles lie near the surface of the ovary, but pass inwards as they increase in size. The large, mature follicles, however, come to lie just below the surface from which they begin to protrude visibly at the approach of the breeding season. During the proœstrum one or more follicles (the number varying in different animals, according to the size of the litter) may generally be seen showing a very considerable protrusion, while in some animals, such as the sow, the appearance of the ovary at this time is not dissimilar to a bunch of grapes.

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[1] According to Popoff (*Arch. de Biol.*, vol. xxvi., 1911) the origin of the interstitial cells may vary with the species (mole, stoat, dog). For description of interstitial cells in the guinea-pig see Atkins (*Anat. Anz.*, vol. xxxix., 1911), and in man see Wolz (*Arch. f. Gynäk.*, vol. xcvii., 1912), and see above, p. 114. See also Schaeffer (*Arch. f. Gynäk.*, vol. xciv., 1911).

[2] Pflüger, *Ueber die Eierstöcke der Säugethiere und des Menschen*, Leipzig, 1863.

[3] Balfour, *loc. cit.*

[4] Lane-Claypon, "On Ovogenesis, etc.," *loc. cit.* That one ovum may develop at the expense of others is particularly well shown in *Hydra*, *Tubularia*, and certain other Cœlenterates. The nuclei of the ingested ova continue to be easily recognisable even during the early segmentation stages of the developing egg.

A large Graafian follicle in a mature ovary contains the following parts: Forming the outermost part of the wall and in continuity with the ovarian stroma is the theca externa, which is a layer of somewhat fibrous connective tissue. Within this is the theca interna, which is less fibrous. The two thecæ are only slightly modified ovarian stroma. Within the theca interna is the epithelial wall, which, in the very young follicles, consists of a single layer of cells immediately surrounding the ovum. These, as already mentioned, multiply rapidly (by mitotic division) and give rise to a layer many cells deep, which, as the follicle increases in size, becomes divided into two layers, the membrana granulosa lining the follicle, and the discus proligerus surrounding the ovum. The innermost cells of the discus rest upon a thick, transparent, radially striated membrane with a granular outer border. This is a zona radiata or zona pellucida. The striated appearance is due to the presence of fine canals. Within the zona, and immediately enclosing the ovum, another very thin membrane can sometimes be made out. This is the vitelline membrane. The membrana granulosa and discus proligerus are united by one or more strands of follicular epithelial cells. A viscid fluid, containing protein matter, collects between them and becomes gradually increased in quantity as the follicle continues to grow.[1]

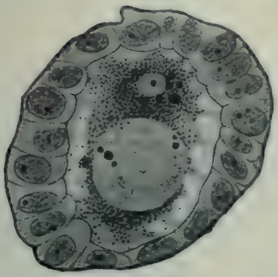

FIG. 34.—Young oöcyte or egg surrounded by a single layer of follicular epithelial cells. (From van der Stricht.)

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[1] Occasionally a Graafian follicle may contain more than one ovum, but this is abnormal. Such follicles have been described as occurring in the rabbit's ovary by Honoré ("Recherches sur l'Ovarie du Lapin," *Arch. de Biol.*, vol. xvii., 1901), and in the dog's ovary by Smyth ("An Unusual Graafian Follicle," *Biol. Bull.*, vol. xiv., 1908). The latter writer states that one follicle contained seven ova. He shows that the tendency to produce multiple ova may be hereditary, and that it is apparently correlated with a high fertility. Multiovular follicles have also been observed in pigs by Corner (*The Corpus Luteum, etc.*, Carnegie Institute (Washington) Publication 222, 1915), and in

According to Walsh[1] the growth energy of the granulosa cells in the guinea-pig is slow in small follicles; then a gradual rise takes place until the follicle attains medium size; later there is a gradual fall in growth energy until in large follicles the proliferative power sinks almost to zero as maturity is reached.

The liquor folliculi begins to form in the developing rat's ovary at about the ninth day of pregnancy.[2] Miss Lane-Claypon suggests that the karyolytic changes which occur in the nuclei of the follicular epithelial cells may have some connection with the origin of the liquor. She states, however, that in the process of formation of the liquor folliculi in the adult ovary, the follicle-cells appear simply to disintegrate and dissolve without showing the phenomena of karyolysis. On the other hand Honoré,[3] who has investigated the subject in the

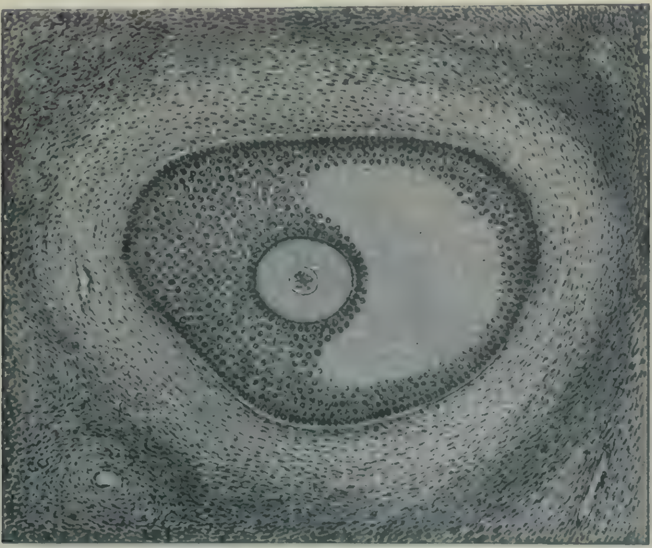

FIG. 35.—Young human Graafian follicle. The cavity contains the liquor folliculi. (From Sellheim.)

Dasyurus by O'Donoghue ("The Corpus Luteum, etc., and Polyovular Follicles in *Dasyurus*," *Anat. Anz.*, vol. xli., 1912). Leo Loeb has discussed the formation of plurioval follicles which he says may originate either by connective tissue failing to grow between the eggs in an early stage, or by very small follicles pushing their way into larger follicles. Both methods depend upon the inactivity of the connective tissue, which is probably due to underfeeding, as Loeb has shown ("The Concrescence of Follicles in the Hypotypical Ovary," *Biol. Bull.*, vol. xxxiii., 1917).

[1] Walsh, "The Growth of the Ovarian Follicle of the Guinea-Pig under Normal and Pathological Conditions," *Jour. Exp. Med.*, vol. xxvi., 1917.

[2] Lane-Claypon, *loc. cit.*

[3] Honoré, "Recherches sur l'Ovarie du Lapin," *Arch. de Biol.*, vol. xvi., 1900.

case of the rabbit, concludes that the liquor folliculi is secreted by the follicle-cells, without their undergoing destruction (or that, if this occur, it is immaterial to the process of liquor formation), in the same way as the urine is secreted by the epithelium of the renal tubules. In support of this view Honoré points out that there are no indications of degeneration or destruction of the follicular epithelial cells of the ripe follicles during œstrus, and moreover, that these cells are retained in the follicle at the time of ovulation, giving rise subsequently to the luteal cells of the corpus luteum. It would appear possible, however, that the liquor folliculi is formed partly by the secretory activity, and partly by destruction of the follicle-cells, just as, according to one view, milk is derived from both the secretion and the disintegration of the cells of the mammary gland (see p. 592).[1]

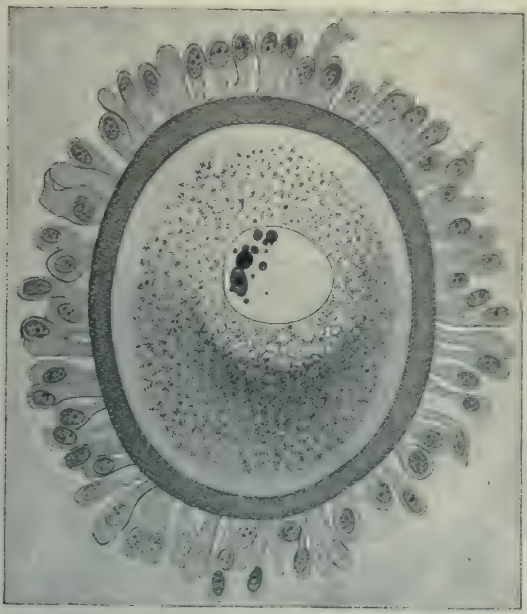

FIG. 36.—Human ovum at termination of growth period. (After van der Stricht.) Yolk granules, vacuoles, and fat drops are seen.

Heape[2] states that during the growth of the ovum nourishment is supplied to it by the aid of the discus proligerus, for fine protoplasmic processes may be seen passing from the cells of this layer and projecting into radiating canals in the zona which encloses the ovum, being in contact with the vitelline membrane.

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[1] For rate of growth in avian ova, see Riddle ("Studies on the Physiology of Reproduction in Birds," *Amer. Jour. of Physiol.*, vol. xli., 1916). Riddle states that yolk formation is not necessarily connected with the production of ova (*Biol. Bull.*, vol. xxii., 1912).

[2] Heape, "The Development of the Mole," *Quar. Jour. Micr. Science*, vol. xxvi., 1886.

Immediately after copulation, and therefore during œstrus, the cells of the discus proligerus (in the rabbit)[1] begin to withdraw radially, and eventually remain attached to the zona radiata by the extremely thin strands just referred to. At the same time the ovum itself withdraws somewhat from the zona, leaving a narrow circular space. These processes occupy some hours. About nine

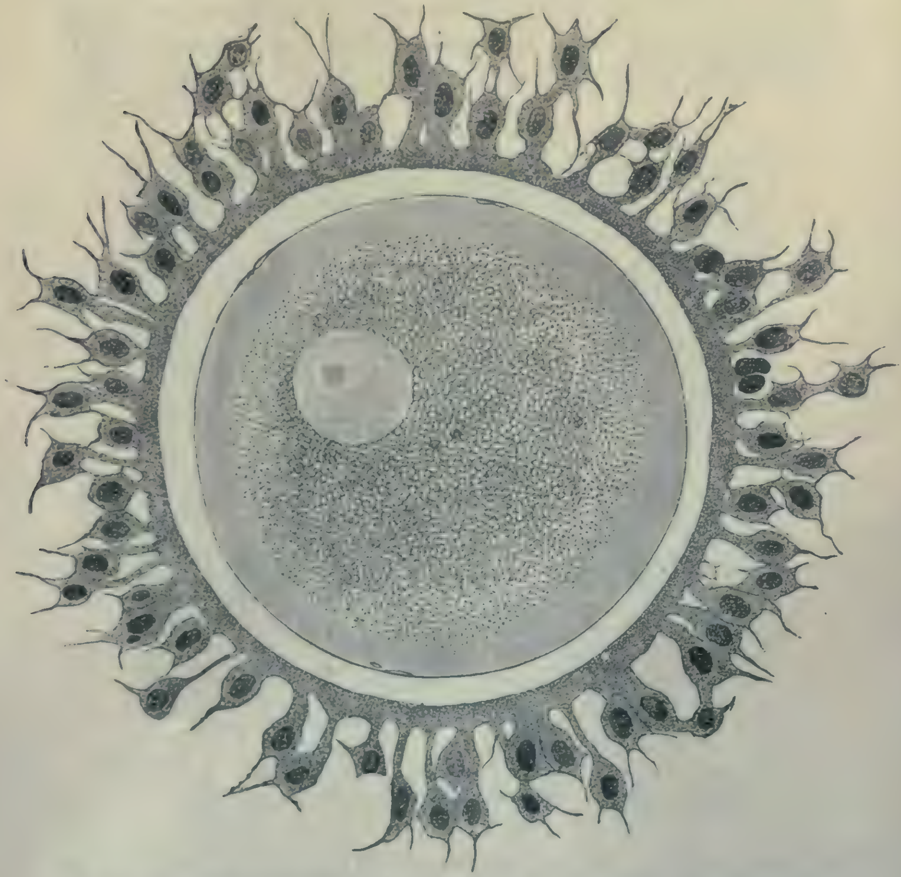

FIG. 37.—Human ovum examined fresh in the liquor folliculi. (From Waldeyer.) The ovum shows yolk granules in the centre surrounding the nucleus (with its nucleolus) and a clearer peripheral portion. It is enclosed by follicular epithelial cells.

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[1] In the rabbit these processes depend on coition. (Heape, "Ovulation and Degeneration of Ova in the Rabbit," *Proc. Roy. Soc.*, B., vol. lxxvi., 1905.)

hours after copulation, when the supply of nourishment has been entirely cut off, the two polar bodies are formed, and the ovum becomes mature.[1]

The essential facts about the maturation process were first ascertained by van Beneden [2] in *Ascaris*, and were afterwards studied more fully by Boveri.[3] Subsequently Montgomery [4] has elucidated the process still further by showing that prior to the formation of the first polar body the chromatin filaments or chromosomes of the cell nucleus conjugate together in pairs, and that in all probability one member of each pair is a descendant of a chromosome derived from the father, while the other member is descended from a corresponding maternal chromosome.[5] The possible significance of this conjugation of chromosomes is referred to on a later page (see p. 201). In the subsequent maturation division the chromosomes again separate.[6]

The changes involved in the formation of the first polar body are in most respects similar to those of ordinary cell division. The centrosome, which lies in the cytoplasm, divides, and the two daughter centrosomes thus produced travel to opposite sides of the nucleus. In the meantime, the latter forms a spindle, the nuclear membrane having disappeared. Each centrosome becomes surrounded by a system of rays, and in this way the attraction spheres are formed. The chromosomes next arrange themselves equatorially between the attraction spheres, each one having now split into two parts. Half of these migrate towards each centrosome, and the nucleus becomes divided. One of the daughter nuclei, together with a thin investment of protoplasm, is extruded from the ovum. This is the first polar body, which is therefore a product of unequal cell division. Subsequently to extrusion it sometimes divides into two. After the formation of the first polar body, the ovum again divides in the same unequal fashion, and the second polar body is formed and extruded. The polar bodies undergo degeneration. Meanwhile the nucleus of the ovum once more becomes surrounded by a membrane and enters upon a resting stage.

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[1] *Cf.* Thomson (A.), "The Maturation of the Human Ovum," and "The Ripe Human Graafian Follicle," *Jour. of Anat.*, vols. liii. and liv., 1919 and 1920.

[2] Van Beneden, "Recherches sur la Maturation de l'Œuf," *Arch. de Biol.*, vol. iv., 1883.

[3] Boveri, "Zellenstudien," *Jenaische Zeitsch.*, vol. xxi., 1887.

[4] Montgomery, "Some Observations and Considerations upon the Maturation Phenomena of the Germ-Cells," *Biol. Bull.*, vol. vi., 1904.

[5] The observations of this author, together with those of Sutton, McClung, Wilson, etc., point to the conclusion that all the nuclei in the somatic cells contain two parallel series of chromosomes (paternal and maternal).

[6] In the reduction process each pair of fused chromosomes becomes divided into a group of four bodies united by linin threads. These are the tetrads or "vierergruppen." It follows that the number of tetrads in any particular species is always one-half the number of somatic chromosomes. Thus, if the somatic cells contain sixteen chromosomes, the number of tetrads formed is eight, while, as shown in the text, the number of chromosomes in the mature germ-cells (after reduction) is also eight.

The process of formation of the first polar body differs from that of the second in that the chromosomes do not undergo splitting. Consequently the nucleus of the mature ovum contains only half the original number of chromosomes. This number varies in the different species, but is constant in each.[1] According to Duesberg it is twenty-four in man, so that in the mature human ovum there should be only twelve chromosomes.[2]

The evidence of other investigators is conflicting, von Winiwarter[3] stating that in the human female there are forty-eight chromosomes and in the male forty-seven. According to Guyer[4] and Montgomery[5] there are in the negro probably only half the number of chromosomes that there are in the white race.

As will be shown in the next chapter, the spermatozoa, or male germ-cells, undergo a similar process of maturation, the conjugating cells containing only half the number of chromosomes characteristic of the species, just as in the case of the conjugating ova.[6] It has been supposed, therefore, that the reduction in the number of chromosomes is a preparation on the part of the germ-cells for their subsequent union, and a means by which the number of chromosomes is held constant in each species.

The discovery that the nuclei of the conjugating cells contain only half the number of chromosomes possessed by the soma or body-cells was made originally by van Beneden. It has since been extended to so many animals and plants that it may probably be regarded as a general law of development.[7]

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[1] Von Winiwarter, however, states that in the rabbit the number varies from thirty-six to eighty, but is generally about forty-two (*Arch. de Biol.*, vol. xvi., 1900).

[2] Duesberg, "Sur le Nombre de chromosomes chez l'Homme," *Anat. Anz.*, vol. xxviii., 1906.

[3] Von Winiwarter, "Étude sur la Spermatogenèse humaine," *Arch. de Biol.*, vol. xxvii., 1912.

[4] Guyer, "Accessory Chromosomes in Man," *Biol. Bull.*, vol. xix., 1910; *Science*, vol. xxxix., 1914.

[5] Montgomery, "Human Spermatogenesis," *Jour. Acad. Nat. Science*, Philadelphia, vol. xv., 1912.

[6] But see below, footnote, p. 166.

[7] For details of the process in various forms of life see Wilson, *The Cell*, 2nd Edition, New York, 1900. See also Doncaster, "On the Maturation of the Unfertilised Egg, etc., in the Tenthredinidæ," *Quar. Jour. Micr. Science*, vol. xlix., 1906; "Gametogenesis, etc.," *Proc. Roy. Soc.*, B., vol. lxxxii., 1910, and vol. lxxxix., 1916. Doncaster shows that in the sawflies there are two types of maturation process, in one of which there is no reduction. It is probable that only the reduced eggs are capable of fertilisation. In other cases, however, the ova are able to undergo parthenogenetic reproduction without forming polar bodies. See Hewitt, "The Cytological Aspect of Parthenogenesis in Insects," *Manchester Memoirs*, vol. lx., 1906; Doncaster,

It is commonly believed that the chromatin material is the substance which has the potentialities of development, and which plays the principal part in perpetuating the hereditary structure and qualities of the particular animal or plant, but there is no real proof that this is effected by them exclusively (see p. 204).

The maturation phenomena may take place within the ovary prior to the discharge of the egg, or they may be postponed until after ovulation has occurred. In the rabbit, as has been shown already, the polar bodies are formed while the ovum is still in the ovary, and the same is believed to be the case in man.[1]

In the case of the mouse, Sobotta[2] came to the conclusion that the first polar spindle is suppressed, and that the second polar body might be formed during the passage of the ovum down the Fallopian tube. Gerlach[3] describes the second polar body as being in some instances suppressed after the entry of the spermatozoön in fertilisation, the second polar spindle degenerating within the egg. Kirkham,[4] however, states that the maturation of the mouse's ovum is in no way exceptional, the process involving the formation of two polar bodies as in most other animals. The first polar body is extruded in the ovary, while the second is given off in the Fallopian tube immediately after fertilisation by a spermatozoön.[5] Rubaschkin[6] has shown that the maturation processes in the guinea-pig are similar. In both the guinea-pig and the mouse, ova which are retained in the ovary, and also those which are discharged and fail to become fertilised, undergo degeneration with the second polar spindle within them.

The maturation phenomena in the bat (*Vesperugo noctula*) have been investigated by van der Stricht, who has published a series of

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"Animal Parthenogenesis," *Science Progress*, vol. iii., (July) 1908 ; and *Cytology*, Cambridge, 1920. These works contain further references.

[1] Thomson (A.), *loc. cit.*, 1919.

[2] Sobotta, "Die Befruchtung und Furchung des Eies der Maus," *Arch. f. Mikr. Anat.*, vol. xlv., 1895.

[3] Gerlach, *Ueber die Bildung der Richtungskörper bei Mus musculus*, Wiesbaden, 1906.

[4] Kirkham, "The Maturation of the Mouse Egg," *Biol. Bull.*, vol. xii., 1907 ; and "The Maturation of the Egg of the White Mouse," *Trans. Connecticut Acad. Arts and Sciences*, vol. xiii., 1907.

[5] Sobotta ("Die Bildung der Richtungskörper bei der Maus," *Anat. Hefte*, vol. xxxv., 1907), in a further paper, expresses himself doubtful as to whether two polar bodies are really discharged in all cases in the maturation process of the mouse's ovum. His own observations lead him to conclude that two polar bodies are discharged in not more than one-fifth of the total number of maturations, only one polar body being formed in the great majority of cases. Lams and Doorme ("Nouvelles Recherches sur la Maturation et la Fécondation de l'Œuf des Mammifères," *Arch. de Biol.*, vol. xxiii., 1907) state that they found two polar bodies expelled in forty-four cases out of forty-eight, the first being always smaller than the second.

[6] Rubaschkin, "Ueber die Reifungs- und Befruchtungsprocesse des Meerschweincheneies," *Anat. Hefte*, vol. xxix., 1905.

papers on the subject.[1] This observer states that there are always two polar bodies formed. The first is extruded in the ovary. The second spindle is formed at about the ovulating stage, and the second polar body is discharged in the interior of the Fallopian tube. The first body is formed in February or March, or sometimes later according to the temperature.[2]

It would seem that in the case of the mole the two polar bodies are discharged while the ovum is still retained within the ovary.[3]

In the pigeon it has been shown that the polar bodies are given off while the ovum is passing down the glandular portion of the oviduct and after the entrance of the spermatozoön. The first polar spindle, however, is formed in the ovarian egg; but it is not definitely known at what stage fertilisation occurs, excepting that it is previous to the time when the egg is clasped by the oviducal funnel.

In the frog the polar bodies are extruded after ovulation has taken place, but the egg is not set free until it has reached a certain stage of maturation, which is preparatory to the discharge of the first polar body. The nucleus undergoes a change, and, in place of being large and watery, consists of a small mass of chromatic substance lying in the protoplasm. An achromatic spindle is developed, and the chromatin becomes arranged in the form of granules at the equator of the spindle. The nuclear membrane disappears with the large watery nucleus. The ova in this condition pass into the oviducts.[4]

In certain Invertebrates (Nematodes, Annelids, and Gasteropods) it has been noticed that the occurrence of the maturation phenomena depends upon the act of fertilisation. For example, in the Japanese Palolo-worm, a marine Polychæt Annelid, Izuka[5] has shown that the first polar body is discharged (after certain preparatory changes) one hour after fertilisation by a spermatozoön, and that the second polar body is extruded fifteen or twenty minutes later. In other animals (*e.g. Amphioxus*), one maturation process takes place before, the other during the entrance of the spermatozoön.[1]

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[1] Van der Stricht, "La Ponte ovarique, etc.," *Bull. de l'Acad. Roy. de Méd. de Belgique*, 1901. *Une Anomalie très intéressante concernant le Développement d'un Œuf de Mammifère*, Gand, 1904. "Les Mitoses de Maturation de l'Œuf de Chauve-Souris," *Mémoire présenté au VIIIe Congrès de l'Assoc. des Anatomistes*, Nancy, 1906.

[2] Van der Stricht says (*La Structure de l'Œuf des Mammifères*, Bruxelles, 1909) that he has seen twenty-two ova at the stage of the second polar spindle within the ovary and twenty-seven at the same stage outside of the ovary, the dates varying in each case from the end of February to the end of April. See below, p. 183, Fig. 58.

[3] Heape, "The Development of the Mole," *Quar. Jour. Micr. Science*, vol. xxvi., 1886. For further information as to maturation phenomena, see von Winiwarter (*loc. cit.*, for man); von Winiwarter and Sainmont (*Nouvelles recherches sur l'ovogénèse*, Liege, 1912, for cat); Van der Stricht ("Vitellegénèse dans l'Ovule de Chatte," *Arch. de Biol.*, vol. xxvi., 1911, for cat); and Corner ("Maturation of the Ovum in Swine," *Anat. Record*, vol. xiii., 1917, for pig); also Athias, *Sobre as Divisoes de Maturacao do Ovulo dos Mammiferos*, Lisbon, 1910.

[4] Morgan, *The Development of the Frog's Egg*, New York, 1897.

[5] Izuka, "Observations on the Japanese Palolo," *Jour. of the Coll. of Science, University of Tokyo*, vol. xvii., 1903.

It would appear from these facts that the maturation processes in many animals only take place as a result of a specific stimulus which may be induced by the act of copulation, or may be caused only by the entry of the spermatozoön into the protoplasm of the ovum. It would seem, on the other hand, that in some animals maturation takes place independently of any stimulus at such time as the follicle has attained to a sufficient degree of ripeness or after it has discharged its ovum.[2]

It has already been shown incidentally that the processes of maturation and ovulation are intimately associated, and that the latter, like the former, is in many animals dependent for its occurrence upon a definite physiological stimulus. The Graafian follicle may rupture when the egg has reached a certain degree of maturity, or it may require the additional stimulus of sexual intercourse before ovulation can be induced.

In the rabbit ovulation takes place about ten hours after coition.[3] The ovum, which is entirely free from follicular epithelial cells, is discharged into the infundibulum which at this time closely invests the ovary. The discharged ovum is incapable of assimilating nutriment unless it becomes fertilised, and if fertilisation is not effected it undergoes degeneration. Heape found that ovulation could not be induced by artificial insemination, nor by any means other than sexual intercourse, and moreover, that intercourse was a sufficient stimulus, even when the progress of the spermatozoa from the vagina into the uterus was artificially stopped, provided that there was no interference with the vascular supply to the ovaries.

It is stated by Weil[4] that ovulation may take place independently of coition in rabbits which have given birth to young just previously, and Iwanoff,[1] in confirmation of this statement, records experiments in which pregnancy was induced in rabbits by the artificial injection of seminal fluid shortly after parturition (*cf.* p. 102).

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[1] See Przibram, *Embryogeny*, English Translation, Cambridge, 1908.

[2] The chemistry of the maturation process is discussed by Mathews ("A Contribution to the Chemistry of Cell Division, Maturation and Fertilisation," *Amer. Jour. of Phys.*, vol. xviii., 1907). This author describes the maturation of the egg of *Asterias* as being inaugurated by the dissolution of the nuclear membrane. If oxygen is withheld the mature egg soon dies. It is believed that an "oxidase" escapes from the nucleus into the cytoplasm on the rupture of the nucleus. The astral radiations disappear if oxygen is withdrawn, but reappear if oxygen is readmitted. It is concluded that the astral figures are the product of three substances: (1) centriole substance; (2) oxidase; and (3) oxygen.

[3] Heape, *loc. cit.* The maturation processes also depend on coition.

[4] Weil, "Beiträge zur Kenntniss der Befruchtung und Entwickelung des Kanincheneies," *Wien. Med. Jahrbuch*, 1873.

In the mouse,[2] the rat,[3] and the guinea-pig,[4] ovulation occurs spontaneously during "heat," and generally, if not invariably, during œstrus.[5]

In the dog ovulation takes place independently of coition after external bleeding has been going on for some days, or when it is almost or quite over; in other words, it occurs during œstrus and not during the proœstrum, or at any rate not during the early stages of the proœstrum.[6] It is probable that the sow also ovulates during œstrus and not during the proœstrum, since it is stated that sows are most successfully served on the second or third day of "heat."[7] Coition, if it occurs earlier, is frequently not followed by conception.[8] From Hausmann's description it would seem that ovulation does not take place prior to coition, but this conclusion is certainly incorrect.[9]

In the ferret ovulation occurs during œstrus, but postponement of coition may bring about the degeneration of the ripe follicles, since they do not usually discharge spontaneously.[10]

Robinson,[11] who has made a very close study of the phenomenon of maturation and ovulation in the ferret, states that the time intervening between insemination and follicular rupture may vary from 30½ hours to 93½ hours.

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[1] Iwanoff, "La Fonction des Vésicles séminales et de la Glande prostatique," *Jour. de Phys. et de Path. Gén.*, vol. ii., 1900.

[2] Sobotta, *loc. cit.* See also Kirkham, "Ovulation in Mammals, etc.," *Biol. Bull.*, vol. xviii., 1910.

[3] Tafani, "La Fécondation et la Segmentation studiées dans les Œufs des Rattes," *Arch. Ital. de Biol.*, vol. ii., 1889. *Cf.* Kirkham, *loc. cit.*

[4] Rubaschkin, *loc. cit.* See also Loeb (L.), "The Cyclic Changes in the Ovary of the Guinea-pig," *Jour. of Morph.*, vol. xxii., 1911.

[5] According to Smith (H. P.) the ovarian cycle in mice varies from sixteen to nineteen days (*Proc. Amer. Assoc. Anat.* (No. 55), *Anat. Record*, vol. xi., 1917). According to Long and Quisno, rats ovulate every ten days (*Science*, vol. xliv., 1916).

[6] Marshall and Jolly, "Contributions to the Physiology of Mammalian Reproduction: Part I. The Œstrous Cycle in the Dog," *Phil. Trans.*, B., vol. cxcviii., 1905.

[7] See Mackenzie and Marshall, "On Ovariotomy in Sows," *Jour. of Agric. Science*, vol. iv., 1912. According to Corner and Ausbaugh, ovulation may occur before the third day of heat, *Anat. Record*, vol. xii., 1917.

[8] Wallace (R.), *Farm Live Stock of Great Britain*, 4th Edition, London, 1907.

[9] Hausmann, *Ueber die Zeugung und Entstehung des wahren weiblichen Eies, etc.*, Hanover, 1840.

[10] Marshall, "The Œstrous Cycle in the Common Ferret," *Quar. Jour. Micr. Science*, vol. xlviii., 1904.

[11] Robinson, "The Formation, Rupture, and Closure of Ovarian Follicles in Ferrets, etc.," *Trans. Roy. Soc. Edin.*, vol. lii., 1918.

Longley has shown that in the cat ovulation takes place only after coition.[1]

Artificial insemination, followed by pregnancy, has been successfully performed on mares, donkeys, and cows.[2] Consequently it may be concluded that these animals ovulate independently of coition. According to Ewart,[3] ovulation in the mare very often does not occur until near the end of the œstrous period.

It has been shown also that the sheep ovulates spontaneously at each of the earlier heat periods of the sexual season, but that there are reasons for believing that during the later periods the stimulating power at the disposal of the ewes may be so reduced that without coition it is incapable of causing ovulation. There is also evidence that when coition occurs at the beginning of an œstrous period, it may provide a stimulus inducing ovulation to take place a few hours earlier than it otherwise would; in other words, that if ovulation has not already occurred during an œstrus, the stimulus set up by coition may hasten the rupture of the follicle.[4] Recently Iwanoff has succeeded in inducing pregnancy in sheep by artificial insemination. (See p. 176).

There can be little doubt that in the great majority of Mammals ovulation, as a general rule, occurs regularly during œstrus. In certain bats, however, copulation is performed during the autumn, whereas ovulation is postponed until the following spring, the animals in the meantime hibernating, while the spermatozoa are stored up in the uterus (see p. 170).[5] The ovary in the winter months (during the hibernating period) is said to be in a state of quiescence, and the exact time for maturation and ovulation depend upon the temperature of the early months of the year, occurring generally in February or March, but sometimes as late as April.[6] Ovulation takes place some days or even weeks after the formation of the first polar body. It would appear, then, that in bats the follicles can discharge spontaneously under the influence of appropriate seasonable stimuli, and without even the occurrence of œstrus.[1]

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[1] Longley, "Maturation of the Egg and Ovulation in the Domestic Cat,' *Amer. Jour. of Anat.*, vol. xii., 1911. Doncaster has recorded that a female cat, after copulating with a sterile tortoiseshell male, secreted milk about four weeks later, and continued to do so for two weeks, but without experiencing pregnancy. This was clearly a case of pseudo-pregnancy comparable to what occurs in *Dasyurus*, the dog, and the rabbit under experimental conditions. See p. 36. ("A Possible Connection between Abnormal Sex-limited Transmission and Sterility," *Camb. Phil. Soc. Proc.*, vol. xvii., 1913.)

[2] Heape, "The Artificial Insemination of Mammals," *Proc. Roy. Soc.*, vol. lxi., 1897. There is direct evidence of spontaneous ovulation in cows.

[3] Ewart, "Studies on the Development of the Horse," *Trans. Roy. Soc. Edin.*, vol. li., 1915.

[4] Marshall, "The Œstrous Cycle and the Formation of the Corpus Luteum in the Sheep," *Phil. Trans.*, B., vol. cxcvi., 1903.

[5] Benecke, "Ueber Reifung und Befruchtung des Eies bei den Fledermäusen," *Zool. Anz.*, vol. ii., 1879. Eimer, "Ueber die Fortpflanzung der Fledermäuse," *Zool. Anz.*, vol. ii., 1879. Van Beneden and Julin, "Observations sur la Maturation, la Fécondation, et la Segmentation de l'Œuf chez les Cheiroptères," *Arch. de Biol.*, vol. i., 1880.

[6] Van der Stricht, "L'Atrésie ovulaire, etc.," *Verhand. d. Anat. Gesell. in Bonn*, 1901. *Les Mitoses de Maturation, etc.*, Nancy, 1906.

There has been a considerable amount of controversy regarding the periods at which ovulation occurs in the Primates, the question being discussed at some length in three papers by Heape.[2] This author has shown that ovulation and menstruation are not associated in monkeys (at any rate not necessarily), and that whereas, in both monkeys and the human species, menstruation may occur periodically all the year round, in monkeys there is a limited season for conception and ovulation; while in civilised woman this period is not limited to any particular time of the year, although there is evidence that primitive man agreed with the lower Primates in having a definite sexual season (during which ovulation occurred). (See p. 64.) Van Herwerden[3] has adduced further evidence which shows that there is no apparent connection between ovulation and menstruation, either in monkeys or in the aberrant lemur, *Tarsius spectrum*. It would seem probable, however, in view of Pocock's observations[4] upon the occurrence of a pronounced post-menstrual œstrus in certain monkeys in the Zoological Gardens, that ovulation may take place at this period (that is, at the close of menstruation).

In the case of the human female there is still a great divergence of opinion in regard to the usual time for the discharge of the ova. Some authors express the belief that ovulation occurs before menstruation, others that it takes place during that process, and others again that it follows menstruation. Hergesell[5] has lately adduced evidence which, in his opinion, points to the conclusion that ovulation precedes menstruation, but the occurrence of corpora lutea of uncertain age in the ovary cannot be regarded as supplying definite proof. There are reasons, on the other hand, for concluding that, primitively at any rate, the most usual period for ovulation in the human female was during a definite œstrus following a pro-œstrum, as in many of the lower Mammals; for the period of most acute sexual feeling is generally just after the close of the menstrual

[1] In some Invertebrata which undergo cyclical changes it has been shown that ovulation occurs only at certain intervals depending upon the general condition of the organism. Thus in the females of certain Crustacea ovulation regularly follows the moult and cannot precede it.—*Science* (New Series), vol. xxv. (Feb. 1907).

[2] Heape, *Phil. Trans.*, B., vol. clxxxv., 1894, and vol. clxxxviii., 1897. *Trans. Obstet. Soc.*, vol. xl., 1898.

[3] Van Herwerden, "Bijdrage tot de Kennis van den Menstruellen Cyclus," *Tijdschr. d. Ned. Dierk. Vereen*, vol. x., 1906.

[4] Pocock, "Notes upon Menstruation, etc.," *Proc. Zool. Soc.*, 1906.

[5] Hergesell, "Das zeitliche Verhalten der Ovulation zur Menstruation," *Inaug. Diss.*, Leipzig, 1905. *Cf.* Nielsen, p. 107.

period (see p. 64), while, according to Raciborsky, this is also the commonest season for fertile coition.[1] Moreover, the facts narrated by Bryce and Teacher, in a recent memoir on the early development and embedding of the human ovum, render it extremely probable that the ovum described had been discharged shortly after the cessation of the last menstruation.[2]

With regard to the question as to whether any special stimulus is necessary to induce ovulation in women, Oliver[3] is of opinion that whereas it sometimes may occur spontaneously, it is more than probable that it "may be and often is accelerated by coitus," since at this time there is "an increased determination of blood to the whole genital tract."[4]

This suggestion receives some support from an experiment by Clark,[5] who caused the rupture of a Graafian follicle artificially in a freshly removed ovary by injecting carmine gelatine into the vessels and so raising the ovarian blood pressure.

The causes which determine the rupture of the Graafian follicle are also discussed by Heape,[6] who is of opinion that this is brought about in the rabbit by the stimulation of erectile tissue, and not simply as the result of internal pressure arising from increased vascularity or a greater quantity of liquor folliculi.[1] In this animal the process must be due to a nervous reflex, induced by the act of copulation. Robinson[2] states that in the ferret ovulation is due to the formation of a secondary liquor folliculi which makes its appearance in the epithelial cells surrounding the ovum and which follows successful insemination. The process is unaccompanied by bleeding. According to Stockard[3] ovulation is caused by congestion of the theca interna, but as has been shown above, in those animals in which the ova are discharged spontaneously, this usually occurs during œstrus, and not during the proœstrum when the congestion of the generative tract is at its height. Moreover, as described below, congestion and hæmorrhage into the cavity of the follicle in the rabbit may occur without rupture, the ovum and epithelial cells being retained and eventually undergoing atrophy. Furthermore, Schochet[4] has expressed the view that ovulation is not mechanical or due to pressure, but occurs as a result of digestive action on the part of the liquor folliculi.

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[1] Raciborsky, *Traité de Menstruation*, Paris. See also Luciani, *Human Physiology*, English Edit., vol. v., London, 1921. Oliver thinks that fertilisation may take place at practically any time in the inter-menstrual period ("Fertilisation Time and the Inception of Gestation in Women," *Edin. Med. Jour.*, 1914. See also Fraenkel, "Ovulation, Konzeption und Schwangerschaftsdauer," *Zeitsch. für Geb. und Gyn.*, vol. lxxiv.; and Tschirdewahn, "Ueber Ovulation, Corpus Luteum und Menstruation," *Zeitsch. für Geb. und Gyn.*, vol. lxxxiii.

[2] Bryce and Teacher, *Contribution to the Study of the Early Development and Embedding of the Human Ovum*, Glasgow, 1908.

[3] Oliver, "A Study of Fertilisation with Reference to the Occurrence of Ectopic Pregnancy," *Edin. Med. Jour.*, vol. liv., 1902.

[4] Pregnancy, and therefore ovulation, have been known to take place before the onset of menstruation. Pregnancy may also occur during amenorrhœa (*e.g.* at the commencement of the menopause) and during the lactation period, when menstruation is often in abeyance. Again, it is stated that ovulation has been noted during infancy, before any of the other indications of puberty have been observed (Webster, "The Biological Basis of Menstruation," *Montreal Medical Journal*, April 1897). Further, it will be shown below (p. 378) that the ovaries can maintain their normal functions after the removal of the uterus. It would seem, therefore, that ovulation *may* occur spontaneously in women, and is not *necessarily* connected with either menstruation, œstrus, or coitus. On the other hand, there is evidence that ovulation is usually dependent upon the occurrence of the sexual orgasm in women. Galabin records a case of a woman who married under the age of twenty, and lived in married life with two husbands in succession, and who, when she had passed the age of forty, experienced the sexual orgasm in coitus for the first time, and from that day dated her first and only pregnancy (*Manual of Midwifery*, 6th Edition, London, 1904). That the orgasm (which is characterised by the erection of the clitoris, etc., accompanied by pleasurable sensations) is not absolutely necessary for conception is shown further by pregnancy occasionally occurring in women who are "impotent."

[5] Clark, "The Origin, Development, and Degeneration of the Blood-Vessels of the Human Ovary," *Johns Hopkins Hospital Reports*, vol. ix., 1900.

[6] Heape, "Ovulation, etc.," *Proc. Roy. Soc.*, B., vol. lxxvi., 1905.

Harper's experiments[5] on the fertilisation of the pigeon's egg elucidate the question somewhat further. This author writes as follows: "When a pair [of pigeons] ready for mating is put together, egg-laying ordinarily ensues at the end of a rather definite period, at the least eight days. The female functions are held in abeyance till the proper stimulus is received from a mate.[6] The maturing of the egg is so exclusively a female function that it seems odd at first thought that an apparent exception should occur to the rule. Of course, we know that the final maturation of the egg, or the giving off of the polar bodies, awaits in most animals the act of fertilisation. But here the effect is produced upon the egg by the entrance of sperms. How mating and the act of copulation [which is repeated at frequent intervals every day at this time] could influence the ripening of the egg in the ovary is another problem. In this connection the curious fact must be mentioned that two female pigeons placed in confinement may both take to laying eggs.[7] The function of ovulation is in a state of tension, so to speak, that requires only a slight stimulus, 'mental' apparently in this case, to set the mechanism to working. At any rate, it is impossible to regard the presence of sperm in the oviduct as an essential element of the stimulus to ovulation, although it may have an important influence in the normal case. Our attention is directed to the various and complex instincts of the male which come under the head of courtship, both before and after mating is effected, as furnishing a part of the stimulus to the female reproductive organs." Harper proceeds to describe a curious habit which is common among pigeons before copulating. The male bird regurgitates some secretion in its throat, and this is taken up by the bill of the female in much the same manner as the young take their food. "It is easy to see that here may be one of the sources of indirect stimulation to the female reproductive organs."

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[1] It has been suggested that the follicle may rupture as a result of the breaking down of the blood-vessels in its wall, and the consequently increased pressure due to the bleeding into the cavity. See Heape.

[2] Robinson, *loc. cit.*

[3] Stockard and Papanicolaou, "The Existence of a Typical Œstrous Cycle in the Guinea-pig," *Amer. Jour. of Anat.*, vol. xxii., 1917.

[4] Schochet, "A Suggestion as to the Process of Ovulation and Ovarian Cyst Formation," *Anat. Record*, vol. x., 1916.

[5] Harper, "The Fertilisation and Early Development of the Pigeon's Egg," *Amer. Jour. of Anat.*, vol. iii., 1904.

[6] In the common fowl, and probably in most other birds, ovulation takes place independently of the male.

[7] I am informed by an experienced breeder of pigeons that if overfed an isolated female may lay a few eggs in the course of a year.

Spallanzani[1] found that whereas the female fire-bellied toad could lay its eggs in the absence of the male, the female fetid toad, if isolated, retained its eggs in the ovaries. The common frog is capable of spontaneous oviposition, at least in some cases.[2]

The exact nature of the mechanism by means of which the discharged ova in the human female are made to pass into the aperture of the oviduct is not certainly known. Rouget[3] believed that the fimbriated end of the Fallopian tube erected and partially enclosed the ovary. Kehrer[4] suggested that the ovum was shot into the open fimbriæ in the act of ejaculation. The motion of the cilia, which line the fimbriated end as well as the interior of the tube, no doubt serve to set up a current which assists in directing the ova. The fimbriæ, therefore, act as an aspirator. Gerhardt,[5] who has paid some attention to the question, concludes that in man and many other Primates a number of factors co-operate to secure the entry of the discharged ovum into the tube. These factors include the erectibility of the fimbriæ, the muscular movements of the same, the ciliary currents on the fimbriæ and tube, and the configuration of the ovarian surface. In other orders of Mammals the process is brought about in various ways. In Monotremes, Marsupials, and Cetaceans the entrance to the tube is relatively large as compared with the size of the ovary. In certain other animals a portion of the peritoneum is used as a common envelope for the ovary and the end of the tube. Thus in the dog and ferret the ovary is enclosed in a sac communicating with the cavity of the tube, so that the discharged ova can scarcely fail to effect an entrance into the uterus. There can be little doubt, however, that in the majority of animals ciliary movement plays an important part in directing the course of the expelled ova.

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[1] Spallanzani, *Dissertations*, English Translation, London, 1784.

[2] Morgan, *The Development of the Frog's Egg*, New York, 1897.

[3] Rouget, "Recherches sur les Organes Erectiles de la Femme," *Jour. de la Phys.*, vol. i., 1858.

[4] Kehrer, "Die Zusammenziehungen des Weiblichen Genitalcanals," *Beiträge zur Vergleich. und Exper. Geburtskunde*, 1864.

[5] Gerhardt, "Studien über den Geschlechtsapparat der Weiblichen Säugethiere: I. Die Ueberleitung des Eies in die Tuben," *Jenaische Zeitsch.*, vol. xxxix., 1905.

Nussbaum[1] has described the eggs of the frog as being carried into the mouths of the oviducts by the motion of the cilia of the cœlomic epithelium. These cilia are said to drive in a forward direction any small bodies lying free in the cœlom. Harper[2] states that in the pigeon the egg is clasped by the oviduct, which at this time displays active peristaltic contractions, as if in the act of swallowing the egg.

There is evidence, however, that ova which are discharged from one ovary do not always pass into the oviduct on the corresponding side. For example, instances have been known of animals with a bicornuate uterus becoming pregnant in the uterine horn on the side opposite to that on which the ovary had discharged (as indicated by the presence of a newly formed corpus luteum). Moreover, it has been recorded that animals from which one ovary had been removed have become pregnant in the uterine horn of the other side, an observation which indicates that the ova which are discharged from one ovary may travel across the peritoneal cavity and enter the Fallopian tube which was connected with the other ovary.[3]

It has been stated that in certain abnormal cases an ovum which escapes altogether into the peritoneal cavity may yet become fertilised, bringing about a condition of abdominal pregnancy. There can be little doubt, however, that abdominal pregnancy is nearly always secondary to tubal pregnancy, and that primary ectopic pregnancy is exceedingly rare. According to Loeb[4] the uterine mucosa is the only form of tissue which is able to produce a decidua in the guinea-pig, and while an ovum in the body cavity may undergo the early stages of development, lack of the proper response on the part of the host-tissue (lack of decidual reaction) renders development of the later stages of extra-uterine growth impossible Blair Bell,[5] however, has described a case of primary abdominal pregnancy in the rabbit where four fœtuses were found attached to the gastro-colic omentum. Gofton [1] has described a case of a cat which was pregnant with six kittens, one in the normal position in the uterus, and the other five in the abdominal cavity. The fœtal envelopes of the abdominal embryos were attached by a sort of placenta to the parietal peritoneum and to the omentum, and one had also an extensive attachment to the fundus of the stomach. According to Webster [2] ectopic pregnancy always originates as tubal pregnancy, the tube subsequently undergoing rupture. Huffman [3] explains extra-uterine pregnancy as due to an embedding in anomalous, but specialised tissues, arising from a rudimentary second uterus or other accessory reproductive organs. Tubal pregnancy is generally believed to be due to inflammatory trouble which interferes in some way with the downward movement of the fertilised ovum,[4] but Loeb and Hunter [5] state that in the guinea-pig it is impossible to bring about tubal pregnancy through a mere retention of the ovum in the Fallopian tube.

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[1] Nussbaum, "Zur Mechanik der Eiablage bei *Rana fusca*," *Arch. f. Mikr. Anat.*, vol. xlvi., 1895.

[2] Harper, *loc. cit.*

[3] *Cf.* Hammond, "On some Factors Controlling Fertility in Domestic Animals," *Jour. Agric. Science*, vol. vi., 1914 (for rabbits and pigs), and Corner, "The Corpus Luteum of Pregnancy as it is in Swine," *Contributions to Embryology*, vol. ii., Carnegie Institute Pub., 1915. Internal migration of ova from one uterine horn to another has been shown to be not uncommon.

[4] Loeb (L.), "The Experimental Production of an Early Stage of Extrauterine Pregnancy," *Proc. Soc. Exp. Biol. Med.*, vol. xi., 1914.

[5] Blair Bell, "Primary Abdominal Pregnancy in a Rabbit," *Proc. Roy. Soc. Med.*, 1911.

Ovarian pregnancy is very rare, although well authenticated.

The Formation of the Corpus Luteum

After the discharge of the ovum from the ovary the ruptured Graafian follicle undergoes a series of changes which result in the formation of the structure known as the corpus luteum.

The fully formed corpus luteum consists of large cells containing a yellow pigment, the luteal cells, separated from one another by an anastomosis of connective tissue which is seen to branch inwards from the surrounding ovarian stroma, and to form a central plug in which there are no luteal cells. This connective tissue contains numerous blood-vessels, so that the fully developed corpus luteum is a highly vascular structure.

Three hypotheses have been put forward regarding the manner of formation of the corpus luteum. That of Paterson,[6] who supposed it to be derived from the blood coagulum left in the cavity of the Graafian follicle after its discharge, gained few or no adherents. The other two theories, those of von Baer[1] and Bischoff,[2] on the other hand, have each received considerable support.

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[1] Gofton, "Ectopic Gestation in a Cat," *Royal Dick Coll. Mag.*, vol. i., 1906.

[2] Webster, *Ectopic Pregnancy*, New York, 1895.

[3] Huffman, "A Theory of the Cause of Ectopic Pregnancy," *Jour. Amer. Med. Assoc.*, vol. lxi., 1913.

[4] Mall, *On the Fate of the Human Embryo in Tubal Pregnancy*, Carnegie Institute (Washington) Pub. No. 221, Washington, 1915.

[5] Loeb and Hunter, "Experiments concerning Extrauterine Pregnancy," *Pennsylvania Med. Bull.*, 1908. For further references the above papers may be consulted.

[6] Paterson, "Observations on Corpora Lutea," *Edinburgh Med. and Surg. Jour.*, 1840.

Von Baer regarded the corpus luteum as an entirely connective tissue structure, in the origin of which the follicular epithelium had no share; while Bischoff concluded that the luteal cells were formed by the hypertrophy of the epithelial cells of the undischarged Graafian follicle. Among the principal supporters of von Baer's view appear the names of Leuckart, His, Kölliker, Slavjansky, Gegenbaur, Benckiser, Schottländer, and Minot. Those who have adopted the alternative theory of Bischoff include Pflüger, Waldeyer, Call and Exner, Beigel and Schulin.[3]

To Sobotta[4] belongs the credit of being the first to deal systematically with the question, and, with the publication of his papers on the corpus luteum in the mouse, the controversy entered upon a new phase. In Sobotta's investigation the material employed was collected upon a definite plan, the animals being killed at known intervals after coition, in reference to the occurrence of which the period of ovulation had been previously determined. In this way there was obtained a large series of corpora lutea representing successive stages of development. The investigation resulted in confirming Bischoff's view that the luteal cells are the much hypertrophied epithelial cells of the undischarged follicle, the connective tissue network being derived from the inner layer of the theca.

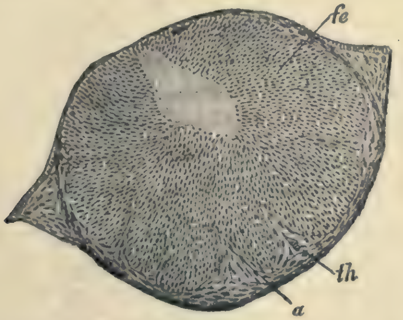

FIG. 38.—Recently ruptured follicle of mouse. (From Sobotta.)

fe, Follicular epithelium or membrana granulosa (somewhat hypertrophied); *th*, theca interna; *a*, ingrowth from same.

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[1] Von Baer, *De Ovi Mammalium et Hominis Genesi Epistola*, Lipsiæ, 1827.

[2] Bischoff, *Entwickelungsgeschichte des Kanincheneies*, Braunschweig, 1842.

[3] For an account of the older literature of the subject see Sobotta, "Über die Entstehung des Corpus Luteum der Säugethiere," Merkel and Bonnet's *Ergebnisse der Anat. u. Entwick.*, vol. viii., 1899.

[4] Sobotta, "Über die Bildung des Corpus Luteum bei der Maus," *Anat. Anz.*, vol. x., 1895; and *Arch. f. Mikr. Anat.*, vol. xlvii., 1896.

Sobotta describes the outer theca as taking no share in the ingrowth, while the theca interna is stated to become entirely spent in the formation of the inter-epithelial anastomosis. The hypertrophy of the epithelial cells is said to be of the nature of a simple enlargement, unaccompanied by division.

Sobotta's conclusions in regard to the development of the corpus luteum in the mouse were subsequently confirmed by him in a further investigation carried out on similar lines on the corpus luteum in the rabbit.[1] Moreover, Stratz[2] published descriptions of certain stages of corpus luteum formation in *Tarsius, Tupaia*, and *Sorex*, and these agree in essential particulars with those given by Sobotta; while Honoré,[3] also working on the rabbit, differed only in concluding that the inter-epithelial network is derived in part from the theca externa, and not exclusively from the theca interna, and that the latter is not entirely exhausted by the ingrowth, some part of it still remaining to form a layer within the outer theca in the fully formed corpus luteum.

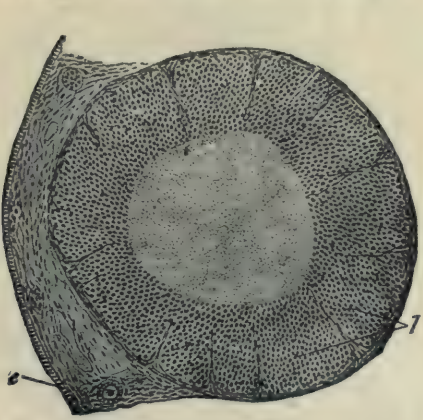

FIG. 39.—Early stage in formation of corpus luteum of mouse. (From Sobotta.)

l, Developing luteal cells ; *e*, germinal epithelium.

On the other hand, several investigators have expressed doubts regarding Sobotta's conclusions, and some have adopted the theory originally formulated by von Baer that the luteal cells arise from the connective tissue sheath of the follicle, the follicular epithelium being either entirely discharged along with the ovum or else being partially discharged and partially degenerating *in situ*. Amongst those who have adopted this view are Nagel,[1] who investigated the human corpus luteum; Clark,[2] who contributed an account of the formation of the corpus luteum in the sow and in the human subject; Doering,[3] who also worked upon the sow, and claimed to have confirmed Clark's account; and Bühler,[4] Wendeler,[5] and Stöckel,[6] who have examined and described developing human corpora lutea. Moreover, His,[7] Kölliker,[8] and Paladino[9] have reiterated their adherence to von Baer's hypothesis since the publication of Sobotta's work.

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[1] Sobotta, "Über die Bildung des Corpus Luteum beim Kaninchen," *Anat. Hefte*, vol. viii., 1897.

[2] Stratz, *Der Geschlechtsreife Säugethiereierstock*, Haag, 1898.

[3] Honoré, "Recherches sur l'Ovaire du Lapin," *Arch. de Biol.*, vol. xvi., 1900.

It is remarkable, however, that none of the supporters of this hypothesis appear to have examined the growing corpus luteum in all its stages of development, while in the case of several of the accounts it is not clear whether the structures described were not in

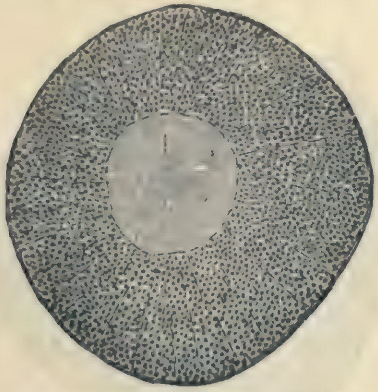

FIG. 40.—Late stage in formation of corpus luteum of mouse. (From Sobotta.) Thecal ingrowths are numerous. The cavity of the follicle is not yet filled in.

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[1] Nagel, "Die Weiblichen Geschlechtsorgane," Bardeleben's *Handbuch der Anatomie des Menschen*, vol. vii., Jena, 1896. "Über neuere Arbeiten auf dem Gebiete der Anatomie der weiblichen Geschlechtsorgane," Merkel and Bonnet's *Ergebnisse d. Anat. u. Entwick.*, vol. viii., 1899.

[2] Clark, "Ursprung, Wachstum, und Ende des Corpus Luteum," *Arch. f. Anat. u. Phys.*, Anat. Abth., 1898; *Johns Hopkins Hospital Reports*, vol. vii., 1899.

[3] Doering, "Beitrag zur Streitfrage über die Bildung des Corpus Luteum," *Anat. Anz.*, vol. xvi., 1899.

[4] Bühler, "Entwickelungsstadien Menschlichen Corpora Lutea," *Verhand. d. Anat. Gesell.*, in Pavia, 1900.

[5] Wendeler, Martin's *Die Krankheiten der Eierstocke und Nebeneierstocke.*

[6] Stockel, "Ueber die Cystiche Degeneration der Ovarien bei Blasenmole," *Sep. Abdruck aus der Festschrift fur Fritsch.*

[7] His, Discussion, *Verhand. d. Anat. Gesell.*, in Tübingen, 1899.

[8] Kölliker, "Ueber Corpora Lutea Atretica bei Säugethieren," *Verhand. d. Anat. Gesell.*, in Kiel, 1898.

[9] Paladino, "Per la Dibuttata Questione sulla Esenza del Corpo Luteo," *Anat. Anz.*, vol. xviii., 1900.

reality atretic follicles—that is to say, follicles which had undergone degenerative changes without ever being discharged. Thus, the words used in a description given by Clark seem to indicate that this author was dealing with the degenerative epithelial cells of an atretic follicle. It seems not impossible also that the young human "corpus luteum" described by Doering was a degenerate follicle; while Kölliker's opinion that the corpus luteum is an entirely connective tissue structure appears to have been founded on the assumption that the changes exhibited by discharged follicles and retrogressive undischarged follicles are identical in character. It is to be noted further that in the investigations of all those writers who have upheld the connective tissue hypothesis, the ages of the developing corpora lutea were unknown, the material having been collected in no case by Sobotta's method of killing the animals at successive intervals after coition.

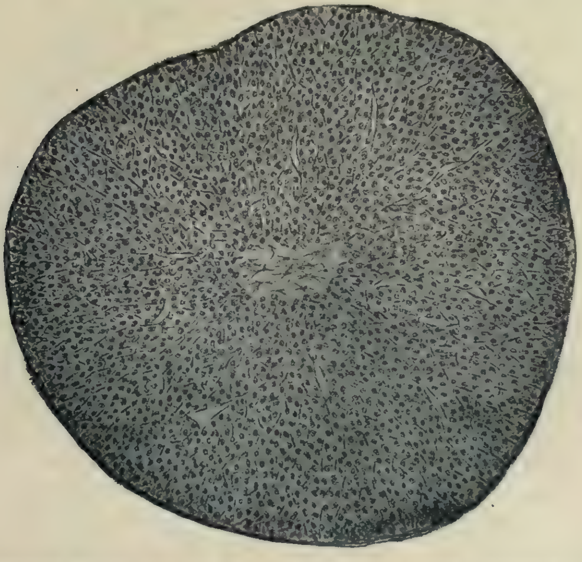

FIG. 41.—Corpus luteum of mouse fully formed. (From Sobotta.) The luteal tissue is vascularised and the central cavity filled in with connective tissue.

In 1901, after the publication of the papers referred to above, the present writer issued a preliminary account[1] of an experimental inquiry upon the formation of the corpus luteum in the sheep. In this inquiry the animals were killed at successive intervals after coition, or (in cases where coition did not or was not known to occur) after œstrus was observed. The result of this investigation was to confirm Bischoff's hypothesis in all essential particulars. The sheep, however, was found to present some differences from the mouse (as investigated by Sobotta) in regard to the origin of the connective tissue network of the corpus luteum, this being discovered to originate partly from the theca externa, and not merely from the theca interna. It was found also that the cells of the follicular epithelium continued to undergo mitotic division after the rupture of the follicle, but not with the same frequency as previously. The theca interna was stated to become entirely spent in the growth of the connective tissue network. Four days after œstrus the discharged follicle was found to have acquired all the characteristics of the fully developed corpus luteum, the luteal cells, as seen in section, being at least six times as large as the original epithelial cells.

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[1] Marshall, "Preliminary Communication on the Œstrous Cycle and the Formation of the Corpus Luteum in the Sheep," *Proc. Roy. Soc.*, vol. lxviii., 1901. The full paper was afterwards published in the *Phil. Trans.*, B., vol. cxcvi., 1903.

In the same year as the publication of the paper referred to above, on the sheep's corpus luteum, van der Stricht[1] gave an account of the discharged follicle in bats belonging to the genera *Vesperugo*, *Vespertilio*, and *Plecotus*. This was also confirmatory of the conclusion that the follicle-cells hypertrophy and give rise to luteal cells, but mitotic division among these cells was also seen to occur. Van der Stricht calls attention to the appearance of fatty particles at a very early stage in the history of the luteal cells. A point of greater importance is that van der Stricht found that, whereas the majority of the luteal cells are derived from the follicular epithelium, a certain relatively small proportion of them are developed out of interstitial cells in the inner theca of the connective tissue sheath. This observation lends additional interest to Miss Lane-Claypon's statement that the follicle and interstitial cells have an identical origin, since both are derived from the germinal epithelium, and pass through a similar series of changes.[2]

The structure of the ovary, and the cyclical changes which it undergoes in the case of the "marsupial cat" (*Dasyurus viverrinus*), have been investigated by Sandes,[3] who shows that the mode of formation of the corpus luteum in Marsupials is essentially similar to what it is in the Eutheria. The theca interna folliculi is shown to be rudimentary in *Dasyurus*, a circumstance which rendered it especially easy to follow the subsequent changes undergone by this layer. Sandes describes the follicular epithelium as undergoing so great an hypertrophy prior to the thecal ingrowth as sometimes almost to fill the cavity of the discharged follicle, so that there could be no possibility of confusing the epithelial with the connective tissue cells.[1]

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[1] Van der Stricht, "La Rupture du Follicule Ovarique et l'Histogénèse du Corps Jaune," *C. R. de l'Assoc. des Anatomistes*, 3rd Session, Lyon, 1901. "La Ponte Ovarique, etc.," *Bull. de l'Acad. Roy. de Médecine Belgique*, 1901.

[2] Marshall, "The Development of the Corpus Luteum: a Review," *Quar. Jour. Micr. Science*, vol. xlix., 1905. Miss Lane-Claypon's discovery that the follicular epithelial and interstitial cells are probably equipotential may perhaps help to elucidate some of the discrepancies between the accounts by various authors of the formation of the corpus luteum.

[3] Sandes, "The Corpus Luteum of *Dasyurus viverrinus*," *Proc. Linnean Soc.*, New South Wales, vol. xxviii., 1903. See also O'Donoghue, "Ueber die Corpora Lutea bei einigen Beuteltieren," *Arch. f. Mikr. Anat.*, vol. lxxxiv., 1914.

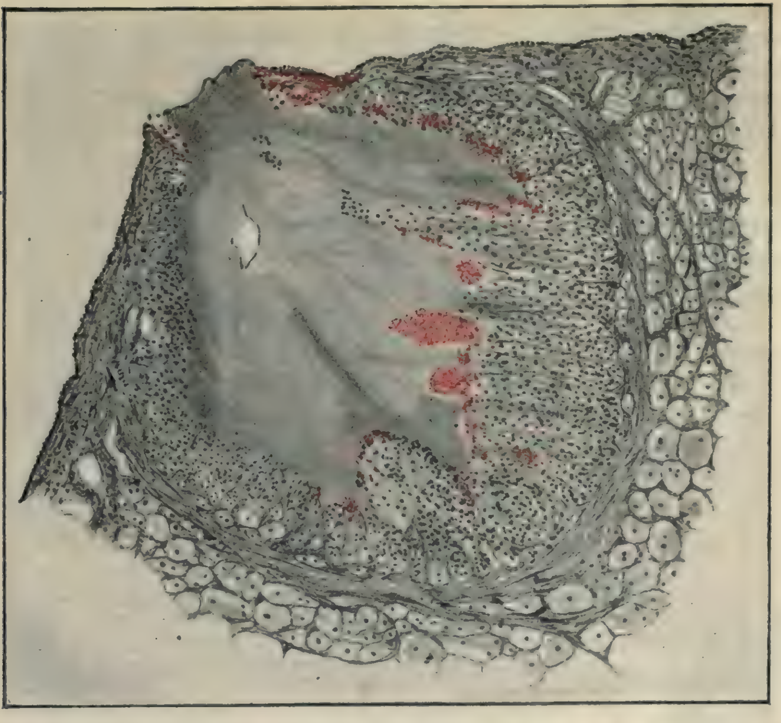

FIG. 42.—Discharged follicle of rabbit nineteen hours after coition, or about nine hours after ovulation. The epithelial cells are in process of hypertrophy and there is some ingrowth of connective tissue from the theca. The place of rupture is widely open. Hæmorrhage is slight. Outside the follicle are old luteal cells of large size. (L. F. Messel.)

The formation of the corpus luteum in the rabbit has been further studied by Cohn,[1] while the same process in the marmot has formed the subject of an investigation by Völker.[2] Both authors agree in supporting Bischoff. Völker finds that the theca externa takes a share in the connective tissue ingrowth, while the theca interna does not become exhausted in the process.

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[1] Through the kindness of Professor J. P. Hill I have been permitted to examine sections in his possession of the corpus luteum of the Monotreme *Ornithorhynchus paradoxus*. These sections show much hypertrophied and apparently fully developed luteal cells, but no trace of any ingrowth from the connective tissue wall of the corpus luteum.

Jankowski,[3] however, has arrived at totally different conclusions, and adopts the view that the luteal cells are modified connective tissue cells. The material employed in this research appears to have consisted of a miscellaneous collection of sows' and guinea-pigs' ovaries obtained without any attempt at systematic investigation, so that the ages of the corpora lutea were unknown. Jankowski bases his opinion largely on the appearance of cells resembling luteal cells in the theca interna of the undischarged follicle. It would seem possible that these were interstitial cells, and so probably potentially equivalent to follicle-cells (as supposed on independent grounds by van der Stricht and Miss Lane-Claypon). More recently Corner[4] has come to the conclusion that in the sow the corpus luteum is formed from both epithelium and theca interna.

Sobotta[5] and Loeb[6] have investigated the formation of the corpus luteum in the guinea-pig, and find, contrary to Jankowski, that it is substantially the same as in the mouse, the rabbit, and the sheep. According to Robinson[7] the luteal cells are formed from the follicular epithelial cells in the ferret.

The results of those investigators who agree in adopting Bischoff's theory of the mode of formation of the corpus luteum may be summarised as follows: The luteal cells represent the epithelial cells of the undischarged Graafian follicle. These, after rupture, undergo a great hypertrophy, which may be accompanied in the earlier stages by mitotic division, but only to a relatively slight extent (*Ovis*, *Vesperugo*, etc.). Meanwhile the thickness of the wall of the discharged follicle is further increased by an ingrowth of connective tissue, which eventually forms an anastomosis of cells, generally fusiform in shape, between the hypertrophying follicular epithelial cells. This connective tissue ingrowth is either derived from the theca interna alone (*Mus*, *Cavia*, *Tarsius*, *Tupaia*, *Sorex*, *Dasyurus*, *Vesperugo*, etc.), or it may arise from both the theca interna and the theca externa (*Lepus*, *Ovis*, *Spermophilus*). The theca interna may become entirely spent in this process (*Mus*, *Cavia*, *Tarsius*, *Tupaia*, *Sorex*, *Ovis*, *Dasyurus*), or certain strands of this layer may still remain and line the outside edge of the follicle after it has become transformed into a fully developed corpus luteum (*Lepus*, *Spermophilus*, *Vesperugo*). In some animals the interstitial cells of the theca interna may develop into luteal cells in just the same manner as the follicular epithelial cells (*Vesperugo*, etc.). The cavity of the discharged follicle becomes filled in eventually by the further ingrowth of connective tissue, which forms a central plug.

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[1] Cohn, "Zur Histologie und Histogenesis des Corpus Luteum und des Interstitiellen Ovarialgewebes," *Arch. f. Mikr. Anat.*, vol. lxii., 1903. Schafer, however, states that in the rabbit the epithelial cells are entirely extruded at ovulation, the cavity becoming filled largely with blood-clot prior to ingrowth from the connective tissue wall (*Essentials of Histology*, 11th Edition, London, 1920). The present writer has reinvestigated the question and finds that the epithelium is retained. The confusion may have arisen through mistaking atrophic follicles for discharged ones (see p. 150).

[2] Völker, "Über die Histogenese Corporis Lutei bei den Ziesel (*Spermophilus citillus*)," *Bull. Internat. Acad. Science* (*Médicine*), Prague, 1904.

[3] Jankowski, "Beitrag zur Entstehung des Corpus Luteum der Säugethiere," *Arch. f. Mikr. Anat.*, vol. xliv., 1904. Williams (*Obstetrics*, New York, 1904) takes up the same position as Jankowski, partly on the ground that "the membrana granulosa presents extensive degenerative changes, and is usually cast off in great part at the time of rupture," and partly because certain cells of the theca interna come to resemble luteal cells prior to ovulation. The former statement is far from proved, and the latter cannot be regarded as conclusive (see text). *Cf.* also Seitz, "Die Follikelatresie," *Arch. f. Gynäk.*, vol. lxxvii., 1906.

[4] Corner, "On the Origin of the Corpus Luteum of the Sow," *Amer. Jour. Anat.*, vol. xxvi., 1919.

[5] Sobotta, "Über die Bildung des Corpus Luteum beim Meerschweinchen," *Anat. Hefte*, vol. xxxii., 1906.

[6] Loeb (L.), "Über die Entwicklung des Corpus Luteum beim Meerschweinchen," *Anat. Anz.*, vol. xxviii., 1906.

[7] Robinson, "The Formation, Rupture, and Closure of Ovarian Follicles in Ferrets," *Trans. Roy. Soc. Edin.*, vol. lii., 1918.

The changes undergone by the discharged follicle have also been studied in certain of the lower Vertebrates. Giacomini,[1] who has investigated the subject in birds, amphibians, and, more particularly, Elasmobranch fishes, describes an hypertrophy of the follicular epithelium consequent upon ovulation. The discharged follicle of *Myliobatis* is described and figured as a glandular body in which the enlarged epithelium is penetrated by an extensive ingrowth of connective tissue and blood-vessels. Wallace[2] gives a somewhat similar account of the spent follicles in the fishes *Zoarces* and *Spinax*. In the latter especially there is a pronounced hypertrophic enlargement of the follicle-cells, associated with thecal ingrowths arrayed in a radial manner. Lucien[3] has described corpora lutea in the reptiles *Anguis* and *Seps*, in which there is a simple hypertrophy of the follicular epithelium unaccompanied by mitotic division. Similar structures in reptiles have also been observed by Mingazzini,[4] who believes them to be identical with mammalian corpora lutea. It is noteworthy that the above-mentioned animals which show luteal hypertrophy are all viviparous. On the other hand, Bühler,[1] who investigated the ovaries of Cyclostomes and certain Teleosteans, was unable to find any hypertrophy of the wall of the spent follicle, and Cunningham,[2] also writing on Teleosteans, arrived at the same result as Bühler. According to Pearl and Boring,[3] however, a corpus luteum is formed in the ovary of the hen after ovulation and simply from the theca interna. It contains a yellow, fatty substance similar to that of the corpus luteum of the cow.

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[1] Giacomini, "Contributo all' Istologia dell' Ovario dei Selaci," *Ricerca Lab. di Anat. Normale della Roy. Univ. di Roma*, vol. v., 1896.

[2] Wallace (W.), "Observations on Ovarian Ova, etc.," *Quar. Jour. Micr. Science*, vol. xlvii., 1903.

[3] Lucien, "Note préliminaire sur les premières Phases de la Formation des Corps Jaune chez certains Reptiles," *C. R. de Soc. de Biol.*, vol. lv., 1903.

[4] Mingazzini, "Corpi Lutei verie falsi da Rettili," *Ricerca Lab. di Anat. Normale della Roy. Univ. di Roma*, vol. iii., 1893.

The mammalian corpus luteum may contain a central clot composed of blood derived from the vessels of the follicular wall which gave way at the time of ovulation. In this case the blood-clot becomes gradually absorbed along with the remainder of the liquor folliculi. On the other hand, there may be practically no hæmorrhage, or the discharged blood may be expelled to the exterior of the ovary (with the greater part of the liquor), remaining as a small clot upon the surface.[4] It would seem probable that the vessels burst as an effect of the released tension consequent upon the rupture of the follicle: but, as already mentioned, it has been suggested that possibly the latter process may itself occur as the result of the pouring out of blood into the cavity. During the early stages of formation of the sheep's corpus luteum leucocytes of the polymorph variety have been observed in great abundance, but in the later stages they disappear, some of them undergoing degeneration. These leucocytes are not extravasated, but wander inwards with the growing strands of connective tissue.[5] Their occurrence should probably be associated with the necessity to dispose of the blood-clot when such is present.

The ingrowth of connective tissue commences a very short time after ovulation, and in the sheep may be seen very distinctly as early as in the seven-hour stage of development. Blood-vessels are carried inwards with the connective tissue, and these undergo multiplication, so that the corpus luteum is a highly vascular structure.

If the discharged ovum fails to become fertilised the corpus goes on growing usually for only a short time and then degenerates, so that, in the case of the human female, two months after ovulation it is reduced to the condition of an insignificant cicatrix. Miller[1] found that in man the beginning of menstruation coincided with the degeneration of the corpus luteum. In polyœstrous animals which ovulate spontaneously the organ is in process of reduction at about the time of the next "heat" period, but two corpora lutea of different ages have been observed in the same ovary. Thus Corner[2] finds that in the sow there is, during the sexual season, a regular overlapping in the duration of these structures, and at any œstrus after the second there are in the ovaries corpora lutea in an advanced stage of degeneration, probably six weeks old, and others, about three weeks old, in a much less retrogressive condition. In Mammals which experience pseudo-pregnancy the corpus luteum under that condition may persist for a considerable time, which is as long, or nearly as long, as if pregnancy had occurred, but Hammond has shown that in the rabbit, in which pseudo-pregnancy only occurs under experimental conditions (see p. 101), the corpora lutea in the later part of gestation are larger than those of pseudo-pregnancy. If conception succeeds ovulation, the corpus luteum continues to increase in size until almost the middle of pregnancy, and in the human female attains to a diameter of nearly an inch in length.

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[1] Bühler, "Rückbildung der Eifollikel bei Wirbelthieren," *Morph. Jahr.*, vol. xxx., 1902.

[2] Cunningham (J. T.), "On the Histology of the Ovary and of the Ovarian Ova in certain Marine Fishes," *Quar. Jour. Micr. Science*, vol. xl., 1897 ; *Hormones and Heredity*, London, 1920.

[3] Pearl and Boring, Sex Studies : "The Corpus Luteum in the Ovary of the Domestic Fowl," *Amer. Jour Anat.*, vol. xxiii., 1918.

[4] It is sometimes stated that the hæmoglobin of the blood-clot is transformed into the yellow pigment (known as lutein) which gives the luteal cells their characteristic colour ; but this is obviously incorrect, since there may be no blood-clot in the follicle, whereas the luteal cells always contain lutein.

[5] Marshall, *Phil. Trans.*, *loc. cit.*

The large size of the completely developed corpus luteum is the more remarkable in that it results to so large an extent from the simple hypertrophy of certain of its constituent cells. The wonderful property which these cells possess of enlarging within a very short time of ovulation is seemingly without a parallel in the physiology of the Vertebrata, and it becomes additionally interesting in view of the almost certain fact that the cells, from which the luteal cells develop, are derived, like the ova, from the original germinal epithelium.

During the later part of pregnancy the corpus luteum becomes reduced in size, the luteal cells degenerating, losing their yellow colour, and eventually (at least in some cases) appearing to become transformed into cells resembling, if not identical with, the ovarian interstitial cells referred to above (see p. 114).[3] At the end of pregnancy the human corpus luteum has a diameter not exceeding half an inch in length. In some animals at any rate (rats, etc.; see p. 149) it may persist during the beginning of the lactation period.

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[1] Miller, "Corpus Luteum, Menstruation, und Graviditat," *Arch. f. Gynäk.*, vol. ci., 1914.

[2] Corner, "Cyclic Changes in the Ovaries and Uterus of the Sow," Carnegie Institution Publication (*Contributions to Embryology*, No. 64), 1921.

[3] Schafer, *Essentials of Histology*, 7th Edition, London, 1907. The similarity between the luteal and interstitial cells has also been remarked upon by Allen, *loc. cit.*

The characteristics of the corpus luteum at different stages of pregnancy have been described by van der Stricht,[1] Corner,[2] and others. At first the luteal cells contain a large quantity of fat or lipoid which is epithelial in nature. This decreases, but at a later stage there is a reappearance of fatty material due to senescence. Before retrogression sets in there is a diversity in the character of the cells, some showing considerable peripheral canalisation while others show only endoplasm.[3] According to Corner the corpus luteum of pregnancy is distinguished from that of ovulation by the more regular and uniform morphology of the former, and the greater infiltration of fat in the latter.

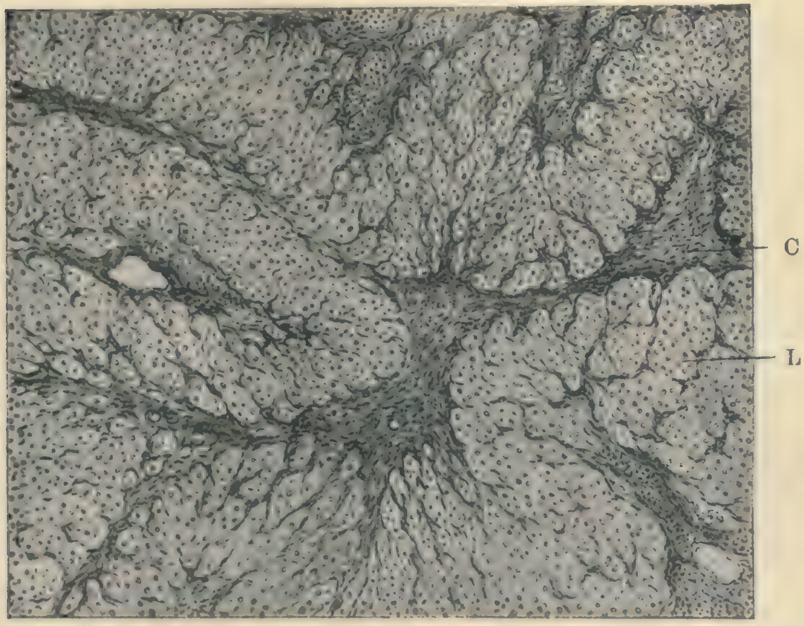

Fig. 43.—Section through old corpus luteum. (From Sellheim.)

C, Connective tissue ; L, luteal tissue.

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[1] Van der Stricht, "Sur le processus de l'excrétion des glandes endocrines," *Arch. de Biol.*, vol. xxvii., 1912-13. This paper deals with bats.

[2] Corner, "The Corpus Luteum of Pregnancy, as it is in Swine," *Contributions to Embryology*, Carnegie Institution, Washington, 1915. This paper goes into great detail and gives numerous references.

[3] See also Delestre, "Recherches sur le Follicle de Graaf et le Corps Jaune de la Vache," *Jour. de l'anat. et physiol.* (etc.), vol. xlvi., 1910 ; Hegar, "Studien zur Histogenese des Corpus Luteum und seiner Rückbildungsprodukte," *Arch. f. Gyn.*, vol. xci., 1910 ; and Drips, "Studies on the Ovary of the Spermophile, etc.," *Amer. Jour. Anat.*, vol. xxv., 1919. The last paper describes three phases (red granules, lipoid droplets, and regression).

In man the corpus luteum eventually loses its colour, becoming converted into the so-called corpus albicans, after which it is described as becoming merged into the connective tissue of the ovary.

The corpus luteum of pregnancy is sometimes distinguished from the structure formed when pregnancy does not supervene after ovulation, the latter being called the false corpus luteum,[1] or corpus luteum of menstruation; but it is obvious that the two bodies are identical in the early stages, and otherwise essentially similar.[2] According to Ancel and Bouin,[3] in animals like the rabbit, which do not ovulate spontaneously during œstrus, these two kinds of corpora lutea are identical throughout. In such animals interstitial cells are believed to replace functionally the "periodic corpus luteum." Hammond,[4] however, as just remarked, has shown that the two kinds of corpora lutea in the rabbit are not identical in size, but that the organs formed under experimental conditions (corpora lutea of pseudo-pregnancy, see p. 101) do not become so large as the corpora lutea of pregnancy.

Watson,[5] and Long and Evans,[6] have described a corpus luteum of lactation in the rat, but Hammond states that a study of suckling rabbits' ovaries does not confirm this, but that nevertheless the corpora lutea may persist for some days after pregnancy terminates (see below, p. 622).

The hypotheses which have been put forward regarding the function of the corpus luteum, and the possible part which this organ plays in the metabolism of pregnancy, will be discussed at some length in a future chapter. (For chemistry of corpus luteum see p. 273.)

The Atretic Follicle

It has been already mentioned that the rabbit, the ferret, and certain other animals do not necessarily ovulate during œstrus in the absence of the male. The follicles, instead of bursting, undergo degeneration (atresia) with their contained ova. Heape[7] has shown that the congested vessels in the wall of the follicle may rupture and pour blood into the cavity, where it forms a clot surrounding the degenerating ovum. The brilliant, suffused red appearance of many of the rabbit's follicles during the early stages of degeneration is said to result from internal bleeding. The first rush of blood into the cavity washes away the epithelium from the wall of the follicle, at the same time disintegrating the theca interna. This rupture of the vessels must be interpreted as of the nature of an attempted ovulation, since it apparently only takes place with mature follicles which would have discharged had coition occurred. In other follicles bleeding does not necessarily take place at all. In section the cavity of the degenerate follicle appears, during the early stages, to be bounded by the theca externa, while the ovum may be seen as a shrunken object no longer enclosed by a discus proligerus.[1] Heape[2] states that the contents of the follicle are gradually absorbed through the agency of ingrowing parenchyma cells and leucocytes. The cavity is eventually filled in by the ingrowth of normal ovarian tissue.

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[1] Or corpus luteum spurium.

[2] The retrogressive changes are similar in both kinds of corpora lutea.

[3] Ancel and Bouin, "Sur les Homologies et la Signification des Glandes à Sécrétion interne de l'Ovaire," *C. R. de la Soc. de Biol.*, vol. lxvi., 1909.

[4] Hammond, "On the Causes Responsible for the Developmental Progress of the Mammary Glands in the Rabbit during the latter part of Pregnancy," *Proc. Roy. Soc.*, B., vol. lxxxix., 1917. This author bases his statements on a number of careful measurements which are duly recorded.

[5] Watson (B. P.), "On the State of the Ovaries during Lactation," *Proc. Physiol. Soc., Jour. of Physiol.*, vol. xxxiv., 1906.

[6] Long and Evans, "The Œstrous Cycle in the Rat, and other Studies in the Physiology of Reproduction," *Anat. Record*, vol. xviii., 1920.

[7] Heape, "Ovulation, etc.," *Proc. Roy. Soc.*, B., vol. lxxvi., 1905.

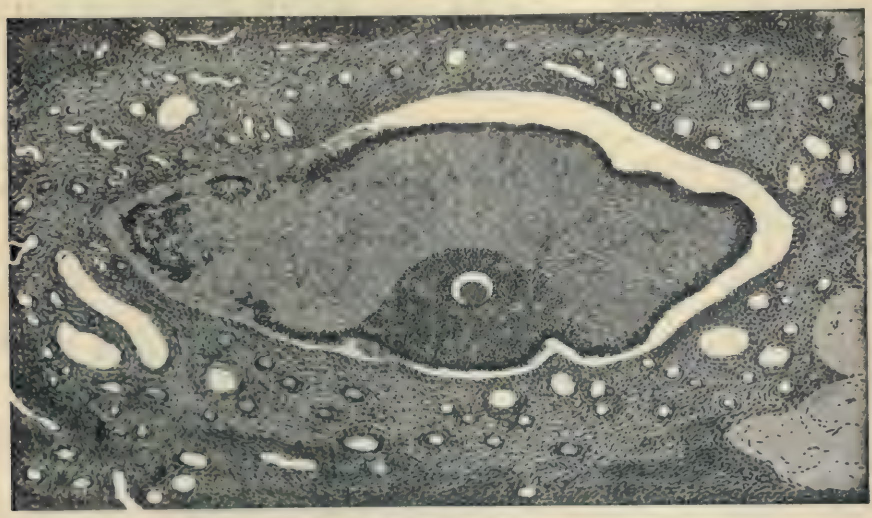

FIG. 44.—Section through follicle in early stage of degeneration. (From Sellheim.) The ovum and follicular epithelium are in process of atrophy.

The following characteristics serve to distinguish the degenerate or atretic follicle (sometimes called the corpus luteum atreticum) from the true corpus luteum: (1) There is no indication of any rupture to the exterior. (2) The ovum, being retained in the follicle, loses its regularly circular shape, becomes shrivelled, and gradually disappears altogether. (3) The follicular epithelium, instead of hypertrophying, degenerates, the chromatic substance at one stage often appearing in the form of fine points in the cytoplasm, and much smaller than nuclei. Subsequently the remains of the cells become unrecognisable, finally disappearing altogether. (4) The connective tissue wall does not proliferate to form a network among the epithelial cells, and there is generally no ingrowth from the thecæ until the epithelial cells are in an advanced state of degeneration or have altogether disappeared. The earliest indication of atretic change is usually seen in the chromatolytic changes in the epithelium. Afterwards the theca interna degenerates, and then the ovum and zona pellucida.

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[1] Marshall, "The Œstrous Cycle in the Common Ferret," *Quar. Jour. Micr. Science*, vol. xlviii., 1904.

[2] Heape, *loc. cit.*

It should be mentioned, however, that the presence of a degenerate ovum cannot, by itself, be regarded as an absolute indication of follicular atresia, since Sobotta[1] has recorded instances of rupture in the mouse and in the rabbit in which the ova were accidentally retained within the cavity of the follicle, the latter nevertheless forming an otherwise typical corpus luteum; and van der Stricht[2] has described a similar case of retention in *Vesperugo*, in which part of the follicle was degenerate while another part possessed the characteristic structure of a corpus luteum.

Degeneration may set in at all stages in the development of a follicle, and not merely in the fully formed follicle which has failed to rupture. Loeb[3] has described follicular atresia as being common in guinea-pigs of less than six months old. Kingsbury[4] has described profound degeneration of certain follicles as occurring just before sexual maturity in the cat. Atrophic follicles which have reached or almost reached maturity (in the rabbit) before undergoing degeneration are characterised by a considerable internal hæmorrhage.

The degenerative changes which such follicles pass through have been studied in various Mammalia (chiefly rabbits, cavies, and other Rodents) by Schulin,[5] Flemming,[6] Schottländer,[7] Henneguy,[8] Janosik,[9]

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[1] Sobotta, *loc. cit.*

[2] Van der Stricht, *Une Anomalie intéressante de Formation de Corps Jaune*, Gand, 1901.

[3] Loeb (L.), "Über hypertrophische Vorgänge bei der Follikelatresie," *Arch. f. Mikr. Anat.*, vol. lxv., 1905.

[4] Kingsbury, "The Morphogenesis of the Mammalian Ovary," *Amer. Jour. of Anat.*, vol. xv., 1914.

[5] Schulin, "Zur Morphologie des Ovariums," *Arch. f. Mikr. Anat.*, vol. xix., 1881.

[6] Flemming, "Ueber die Bildung von Richtungsfiguren in Säugethieren beim Untergang Graafschen Follikel," *Arch. f. Anat. u. Phys.*, Anat. Abth., 1885.

[7] Schottländer, "Beitrag zur Kenntniss der Follikelatresie, etc.," *Arch. f. Mikr. Anat.*, vol. xxxvii., 1891. "Ueber den Graafschen Follikel, etc.," *Arch. f. Mikr. Anat.*, vol. xli., 1893.

[8] Henneguy, "Recherches sur l'Atrésie des Follicules de Graaf, etc.," *Jour. de l'Anat. et de la Phys.*, vol. xxx., 1894.

[9] Janosik, "Die Atrophie der Follikel," *Arch. f. Mikr. Anat.*, vol. xlviii., 1896.

Kölliker,[1] van der Stricht,[2] Seitz,[3] Loeb, and certain other writers, whose results are for the most part in general agreement. The degenerate follicle in the cow has been described by Delestre.[4]

Schulin, and also Janosik, appear to regard the follicular epithelial cells as being converted into leucocytes, which they undoubtedly resemble when undergoing degeneration. Flemming, on the other hand, denies the existence of leucocytes, pointing out that none exist in the theca, and Schottländer clearly distinguishes degenerating epithelial cells from leucocytes.

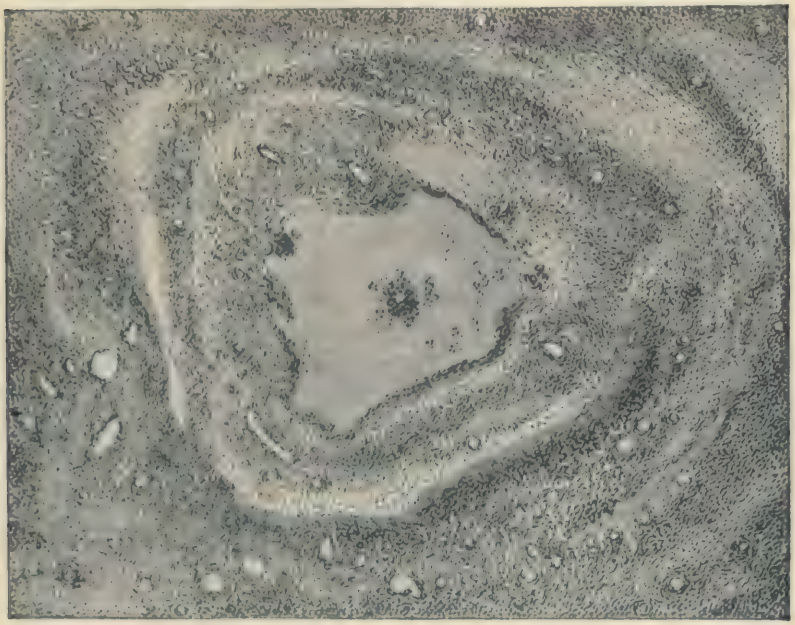

FIG. 45.—Section through follicle in late stage of degeneration. (From Sellheim.) The cavity is in process of being filled by an ingrowth of tissue from the wall. The ovum has disappeared.

More recently, however, Dubuisson[5] has stated that in the sparrow the follicle-cells may multiply and act as phagocytes to the yolk of the degenerating ovum, which becomes filled with them. Afterwards they are said to migrate, leaving nothing but connective tissue which fills in the cavity of the follicle. A similar process is described as occurring in certain reptiles. Perez[1] also has recorded the phagocytic absorption of ova by follicle-cells in the ovary of the fasting newt.

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[1] Kölliker, "Über Corpora Lutea Atretica bei Säugethieren," *Verhand. d. Anat. Gesell.*, in Kiel, 1898.

[2] Van der Stricht, "L'Atrésie Ovulaire, etc.," *Verhand. d. Anat. Gesell.*, in Bonn, 1901.

[3] Seitz, "Die Follikelatresie während der Schwangerschaft, etc.," *Arch. f. Gynäk.*, vol. lxxvii., 1906.

[4] Delestre, *loc. cit.* See also Athias, "Les phénomènes de division de l'ovule, etc.," *Anat. Anz.*, vol. xxxiv., 1909; and Asimi, "Observations on Follicular Atresia, etc.," *Anat. Record*, vol. xviii., 1920.

[5] Dubuisson, "Contribution à l'Étude du Vitellus," *Arch. de Zool. Expér.*, vol. v., 5th series, 1906.

Schottländer[2] states that atresia can occur by fatty degeneration as well as by chromatolysis.

Flemming and others have described nuclear spindles in the ova of follicles in an early stage of atresia, thus showing that these had reached maturity before degeneration set in.

Atretic follicles may shrivel up rapidly, or continue for a time in a cystic condition. In the latter case the cavity remains filled with fluid. Kölliker has shown that certain of the cells in the theca interna of cystic follicles may undergo a process of hypertrophy; and the same fact has been noticed by Seitz, who calls these cells "theca lutein cells" owing to their resemblance to the cells of the corpus luteum. Seitz found these cells only during pregnancy. Leo Loeb[3] also says that in the rabbit the theca interna cells may enlarge during atresia, becoming epithelioid and gland-like and that they remain in this condition for some time.

Heape[4] states that in the rabbit two kinds of degeneration prevail. In the one kind the changes first affect the follicle and then the ovum, as described above. In the other the ovum is first affected and the follicle afterwards. Heape interprets the latter change as evidence that the ovum is not capable of assimilating the nourishment supplied to it.

Atresia is commonly stated to occur most frequently during pregnancy, but it may occur at other times.[5] Thus Sandes[6] has shown that in *Dasyurus*, as soon as the corpus luteum is formed, the surrounding follicles which were previously in various stages of active development begin to undergo atrophy. The process begins in the follicles in closest proximity to the newly formed corpus luteum, and is continued during pregnancy in the other follicles in ever-widening circles. Sandes suggests that this occurs as a result of mechanical pressure due to the growth of the corpus luteum, or is in some way effected by the internal secretion which the latter organ is supposed to elaborate. Heape[1] states that in the case of the rabbit, if the buck is withheld from a doe during several consecutive œstrous periods, not merely the majority of the older follicles degenerate, but also many of the younger ones, so that the animal is liable to become sterile during the remainder of the breeding season.[2]

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[1] Perez, "Sur la Résorption phagocytaire des Ovules, etc.," *Procès-Verbaux de la Soc. des Sciences de Bordeaux*, 1903.

[2] Schottländer, *loc. cit.*

[3] Loeb, "The Relation of the Ovary to the Uterus and Mammary Gland," *Trans. Amer. Gyn. Soc.*, 1917.

[4] Heape, *loc. cit.*

[5] Marshall, "The Œstrous Cycle, etc., in the Sheep," *Phil. Trans.*, B., vol. cxcvi., 1903.

[6] Sandes, *loc. cit.*

There can be little doubt that the more usual cause of degeneration in immature follicles is lack of sufficient nutriment, or of nutriment of the requisite kind. It is usually to be observed in underfed animals, or in animals living under unsuitable conditions, but it also occurs in very fat animals. Ewart states that follicular degeneration tends to occur in mares leading a semi-wild life in winter.[3] Probably it is least common in animals which are in a good thriving condition, but further investigation is urgently needed before these points can be decided.

SUPERFŒTATION

In the majority of Mammals, as in *Dasyurus*, there can be little doubt that the presence of the corpus luteum tends to produce follicular degeneration, or at any rate to inhibit maturation. In the mare, however, Ewart has shown that degeneration does not generally take place during early pregnancy, so that if a mare aborts (a common occurrence with this animal) ripe ova are available for fertilisation, and pregnancy can be started anew without delay.[4]

If ovulation takes place during pregnancy, and if, owing to the occurrence of coition (see p. 33), the ova become fertilised, the phenomenon of superfœtation may take place — that is to say, fœtuses of different ages may be present in the same uterus—but this condition is of course abnormal, though it has been known to occur in several animals. Thus, Mr. W. O. Backhouse has informed me of a case of a cat which experienced heat and underwent coition after being pregnant for six weeks, and three weeks later produced five kittens, four of which were of the normal size and were obviously born at full time (dating from the heat period prior to the beginning of pregnancy), whereas the other kitten was very small, and apparently about three weeks developed.

Kuntz, however, has pointed out that the existence of fœtuses of varying sizes is not necessarily evidence of superfœtation, since the smaller fœtuses may be atrophic.[5]

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[1] Heape, *loc. cit.*

[2] *Cf.* Dubreuil and Regaud (*C. R. de la Soc. de Biol.*, vol. lxvii., 1909), who say that absence of sexual intercourse causes hæmorrhage in the follicles.

[3] Ewart, *loc. cit.*

[4] *Ibid.*

[5] Kuntz, "Retention of Dead Fœtuses *in Utero* and its Bearing on the Problems of Superfœtation," *Anat. Record*, vol. xviii., 1920. *Cf.* Hammond, see below, Chapter XIV., p. 657.

Formation of Ova

It is usually stated that all the ova which are to be developed in the ovary exist in it at the time of birth, and that a considerable proportion of these undergo atrophy before puberty. Thus, the number of ova in the ovary at birth has been estimated at 100,000, of which it is supposed that not more than 30,000 remain at puberty.[1]

Miss Lane-Claypon,[2] however, has described the formation of ova, resembling primordial ova, from interstitial cells during adult life. These cells are shown to increase markedly in size, their length being often almost doubled. In addition to their becoming enlarged, certain of the interstitial cells near the periphery undergo further changes during the later stages of pregnancy. The cells appear to pass outwards and become cut off by connective tissue, and in many cases almost reach the surface of the ovary. This process begins in the rabbit at about the twentieth day of pregnancy. A little later some of the cells appear to be multi-nucleated, and it is suggested that these are formed by the fusion of the same number of interstitial cells as there are nuclei. The nuclei then degenerate with the exception of one, and the inference is drawn that the latter lives and grows at the expense of the others in just the same way as Balfour concluded that one developing ovum in the immature ovary might be nourished by the surrounding ova which were undergoing degeneration.

In the ovary of a rabbit whose time of parturition had nearly arrived, the interstitial cells were observed to have undergone further changes identical with those taking place in the deutobroque cells of a young ovary during the period of oögenesis (see above, p. 116). The leptotenic stage is rapidly passed through and the nucleus enters upon the synaptenic condition, which extends over a somewhat longer time. The massing of the chromatin into a lump having been completed, it again becomes spread out and rearranged, and the pachytenic stage is entered upon. The chromatin filaments during this stage are markedly thicker and more bulky. It is followed by a not very typical diplotenic stage, in which the duality of the filaments is said to be not well shown. In the next stage—the dictyate stage—the nucleolus becomes very definite, and the chromatin is arranged more or less over the entire nuclear area, which is now of considerable dimensions. "There can be . . . not much doubt that the changes taking place are identical with those seen in the young ovary, which lead to ovogenesis, and therefore it would appear that ovogenesis also takes place in the adult animal during pregnancy."[1]

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[1] Galabin, *A Manual of Midwifery*, 6th Edition, London, 1904. According to another calculation the human ovary at the age of seventeen contains 17,600 ova (Heyse, *Arch. f. Gynäk.*, vol. liii., 1893), of which only 400 become mature (Helne, *Handbuch der Anatomie*, 1873).

[2] Lane-Claypon, "On the Origin and Life-History of the Interstitial Cells in the Ovary in the Rabbit," *Proc. Roy. Soc.*, B., vol. lxxvii., 1905.

Thus it would seem that the interstitial cells, which, like the ova, are almost certainly derived from the germinal epithelium, are actually potential ova, being capable of developing into true ova when the appropriate stimulus is given. This stimulus is provided by pregnancy, at which period they undergo enlargement so as to exceed the size of a primordial ovum, and in addition pass through the same series of nuclear transformations as those which characterise embryonic oögenesis.[2]

THE SIGNIFICANCE OF THE PROŒSTROUS CHANGES

Having discussed the conditions under which the Graafian follicles ripen and discharge in various species of the class Mammalia, we are now in a position to consider more fully the significance of the uterine changes with which ovulation is frequently associated.

Many obstetricians have adopted the view that the degeneration stage of menstruation in the human female is of the nature of an undoing of a preparation (represented by the previous growth stage) for an ovum which failed to become fertilised (or even to be released from the ovary). This theory was originally put forward by Sigismund,[3] and was subsequently accepted by His.[4] It has been summarised in the well-known dictum that "women menstruate because they do not conceive." It has been shown above, however, that menstruation in the Primates is the physiological homologue of the procœstrum in the lower Mammalia, and that ovulation in the latter occurs usually, so far as is known, during œstrus, or at any rate not until after the commencement of the destruction stage of the procœstrum. Consequently Sigismund's theory becomes untenable.

It is possible, however, that in man the breaking-down stage represents pseudo-pregnant degeneration as well as procœstrous destruction owing to the two processes having become telescoped into one another as a consequence of the shortening of the cycle, while, as Hammond points out, the uterine congestion in the rabbit is greatest at the end of pseudo-pregnancy and just before the onset of a new œstrous period. In the monœstrous dog, however, procœstrous destruction and pseudo-pregnant degeneration are distinct.

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[1] Lane-Claypon, *loc. cit.*

[2] Cesa-Bianchi (*loc. cit.*) comments on the close resemblance between luteal and interstitial cells.

[3] Sigismund, "Ideen über das Wesen der Menstruation," *Berliner Klin. Wochenschr.*, 1871.

[4] His, *Anatomie Menschlicher Embryonen*, 1880.

Loewenthal[1] advanced the somewhat different theory that the monthly bleeding is actually brought about by the death of the ovum in the uterus, the "decidua" of menstruation being produced by the embedding therein of the unfertilised egg. No evidence has been adduced in support of this view, which is evidently open to the same objection as Sigismund's hypothesis.

A further modification of the same theory has been advanced by Beard,[2] who expresses the belief that the process of menstruation is of the nature of an "abortion of something prepared for an egg given off at or after the close of the preceding menstruation, and [that] it takes place because this egg has escaped fertilisation." "Prior to the appearance of the menses the uterus has formed a decidua, which is regarded as equivalent to that which would arise when a fertilised egg became affixed to the uterus." This theory also, if it is to be entertained at all, necessitates the assumption that there is no correspondence between the procœstrum in the lower Mammalia and menstruation in the Primates, since the degeneration stage of the procœstrum in the dog or ferret, for instance, can hardly be of the nature of an abortion of something prepared for an ovum which was discharged at the preceding "heat period" many months before. The difficulty is further increased for those animals which experience œstrus only once a year, or even less often, for it is improbable that they ovulate more frequently than they come "on heat." Beard, however, denies that there is any correspondence between "the heat or rut of mammals" and menstruation in the higher forms, saying that very little is required in disproof of the supposed relation.

The theory that the whole procœstrous process, including both the degeneration and the recuperation stages, is of the nature of a preparation[3] on the part of the uterus for the reception of a fertilised ovum is not opposed to any of the known facts. The process is sometimes viewed as a kind of surgical "freshening" of the uterus, whereby the ovum can be safely attached to the mucosa during the healing stage. It is possible, however, that the changing of the uterine tissue is not the least important part of the process.

Emrys-Roberts[4] has made the further suggestion that the secretion of the uterine glands, together with the blood and other products of proœstrous destruction, may serve to provide a rich pabulum on which to nourish the embryo during the earliest days of pregnancy.

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[1] Loewenthal, "Eine neue Deutung des Menstruationsprocesses," *Arch. f. Gynäk.*, vol. xxiv., 1884.

[2] Beard, *The Span of Gestation and the Cause of Birth*, Jena, 1897.

[3] Kundrat and Engelmann, "Untersuchungen über die Uterusschleimhaut," *Stricker's Med. Jahr.*, 1873. Lawson Tait, *Diseases of Women*, 1889. For a further discussion of some of the theories regarding the purpose of menstruation, see Heape, "The Menstruation of *Semnopithecus entellus*," *Phil. Trans.*, B., vol. clxxxv., 1894.

[4] Emrys-Roberts, "A Preliminary Note upon the Question of the Nutrition of the Early Embryo," *Proc. Roy. Soc.*, B., vol. lxxvi., 1905.

In opposition to these theories it may be urged that pregnancy has been known to take place in women who have never menstruated, and that it may occur during periods of amenorrhœa, or during the lactation period, when menstruation is sometimes in abeyance. Such cases, however, are the exception, and it must not be inferred that, because the proœstrous function can occasionally be dispensed with without inducing a condition of sterility, it normally plays no part in the physiology of generation.

It has been pointed out, however, that the severity of the menstrual process in woman is occasionally so great as to be positively injurious, and that such cases evidently belong to the category of constitutional disharmonies which Metchnikoff[1] has shown to be so common in the organs and functions of the generative system.

Geddes and Thomson[2] also have called attention to the pathological character of menstruation, as evidenced not only by the pain which frequently accompanies the process, and the local and constitutional disorders by which it is often attended, but by the general systemic disturbance which always occurs synchronously with it. These authors interpret the discharge as a means of disposing of the anabolic surplus which is consumed during pregnancy by the developing embryo. A similar view is adopted by Webster,[3] who associates the introduction of menstruation (as distinguished from the proœstrum of the lower animals) with a diminished fertility.

Reference has already been made to the "Wellenbewegung" or "wave" hypothesis regarding the nature of menstruation (see p. 61).[4]

The physiological cause of the proœstrum, and the probable part played by the ovaries in this connection, will be discussed at some length in a later chapter.

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[1] Metchnikoff, *The Nature of Man*, London, 1903.

[2] Geddes and Thomson, *The Evolution of Sex*, Revised Edition, London, 1901.

[3] Webster, "The Biological Basis of Menstruation," *Montreal Med. Jour.*, April 1897.

[4] The cyclical changes in the size of the ovaries are referred to on pp. 22 and 53 (footnote).

CHAPTER V

SPERMATOGENESIS—INSEMINATION

"Semper enim partus duplici de semine constat."—LUCRETIUS.

THE spermatozoa, or reproductive cells of the male, were observed as far back as the year 1677, when Hamm, who was a pupil of Leeuwenhoek, directed the latter's attention to them. Leeuwenhoek, however, did not understand the significance of what he saw.

Spallanzani[1] was the first to show that the presence of spermatozoa in the semen was an essential factor in fertilisation, since the filtered fluid was found to be impotent. Subsequently Kölliker[2] discovered that the sperms arise from the cells of the testis, and Barry[3] observed the conjugation of sperm and ovum in the rabbit.

Van Beneden's discovery that the nuclei of the conjugating cells —both ova and spermatozoa—contain only half the number of chromosomes that they had originally has been referred to in the preceding chapter, where the maturation phenomena in the ovum have been briefly outlined[4] (p. 125). The four products of division formed at the completion of reduction in the male differ from those in the female in that each of them is a functional conjugating cell. Before describing the reduction process in detail it will be well to give a short account of the structure of the testis.[5]

This organ is enclosed within a fibrous capsule, the tunica albuginea, which is very rich in lymphatics. It is covered by a layer of serous epithelium reflected from the tunica vaginalis. Posteriorly the capsule is prolonged into the interior of the testis in the form of a mass of fibrous tissue (the mediastinum testis). Certain other fibrous processes or trabeculæ also project inwards from the capsule, and divide the glandular substance into lobules. The efferent ducts of the testis (vasa efferentia) open into a single convoluted tube situated at the posterior margin of the organ and attached to the mediastinum. This is the epididymis. Its lower extremity is prolonged into a thick-walled muscular tube (the vas deferens) which is the passage of exit for the seminal fluid or sperm-containing secretion. The glandular substance of the testis is composed of the convoluted seminiferous tubules, two or three of which join together to form a straight tubule which passes into the body of the mediastinum. The straight tubules within the mediastinum unite in their turn, giving rise to a network of vessels called the rete testis. From the rete the vasa efferentia are given off. Between the tubules is a loose connective tissue containing a number of yellow epithelioid interstitial cells. The connective tissue also contains numerous lymphatics and blood-vessels (branches of the spermatic artery). The nerves of the testis are derived from the sympathetic system, but a few filaments come from the hypogastric plexus.

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[1] Spallanzani, *Dissertations*, English Translation, vol. ii., London, 1784.

[2] Kölliker, *Beiträge zur Kenntniss der Geschlechtsverhältnisse, etc.*, Berlin, 1841.

[3] Barry (M.), "Spermatozoa observed within the Mammiferous Ovum," *Phil. Trans.*, 1843.

[4] For accounts of the history of the chief discoveries relating to the spermatozoa, fertilisation, etc., see Thomson, *The Science of Life*, London, 1899, and Geddes and Thomson, *The Evolution of Sex*, 2nd Edition, London, 1901.

[5] See Barry (D. T.), "The Morphology of the Testis," *Jour. of Anat. and Phys.*, vol. xliv., 1910.

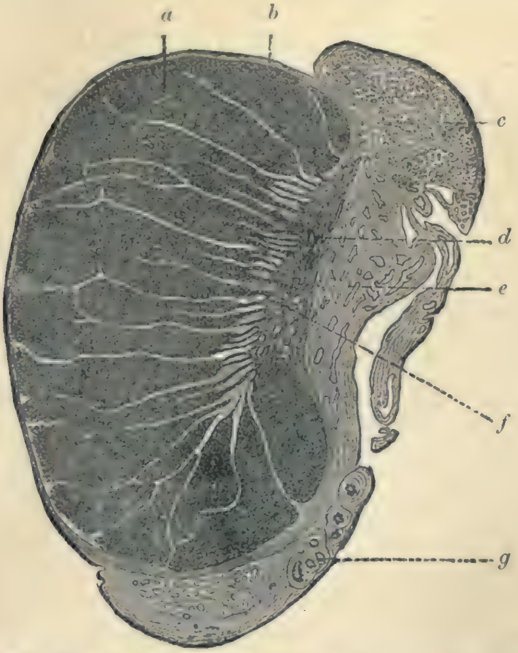

FIG. 46.—Section through human testis and epididymis. (After Bohm and von Davidoff, from Schafer.)

a, Glandular substance divided into lobules by septa of connective tissue; *b*, tunica albuginea; *c*, part of epididymis; *d*, rete testis; *e*, body of epididymis; *f*, mediastinum; *g*, sections through commencing portion of vas deferens.

In embryonic development the tubules arise from the primitive germinal epithelium. According to Allen[1] the interstitial cells are derived from connective tissue.

The straight tubules, and the tubules of the rete, are lined by a single layer of cubical or flattened epithelium without a basement-membrane. The seminiferous tubules, on the other hand, contain several layers of epithelial cells supported by a thick basement-

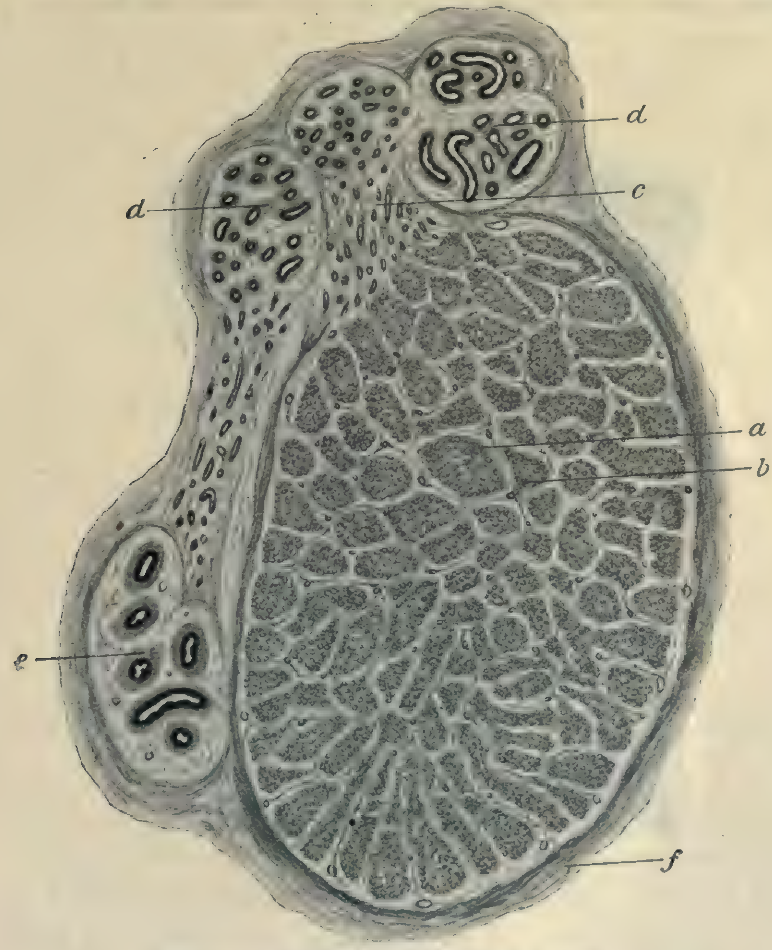

FIG. 47.—Section through testis of monkey.

a, Seminiferous tubules ; *b*, interstitial tissue ; *c*, rete testis ; *d*, vasa efferentia ; *e*, vas deferens ; *f*, tunica albuginea.

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[1] Allen, "The Embryonic Development of the Ovary and Testis," *Amer. Jour. of Anat.*, vol. iii., 1904. As already mentioned, Allen regards the interstitial cells of the ovary as being developed from connective tissue, thus differing from Miss Lane-Claypon.

membrane.[1] The layer nearest the membrane consists of clear cubical cells, a few of which show evidence of division. These are the spermatogonia. Certain of the epithelial cells between the spermatogonia are enlarged, and project among the more internal cells in association with developing sperms. These are the cells of Sertoli. On the inside of the spermatogonia are certain larger cells, known as spermatocytes. These are products of division of spermatogonia, each of which on dividing into two gives rise to a cell like itself, and another cell, which grows larger, passes into the second layer, and becomes a spermatocyte.

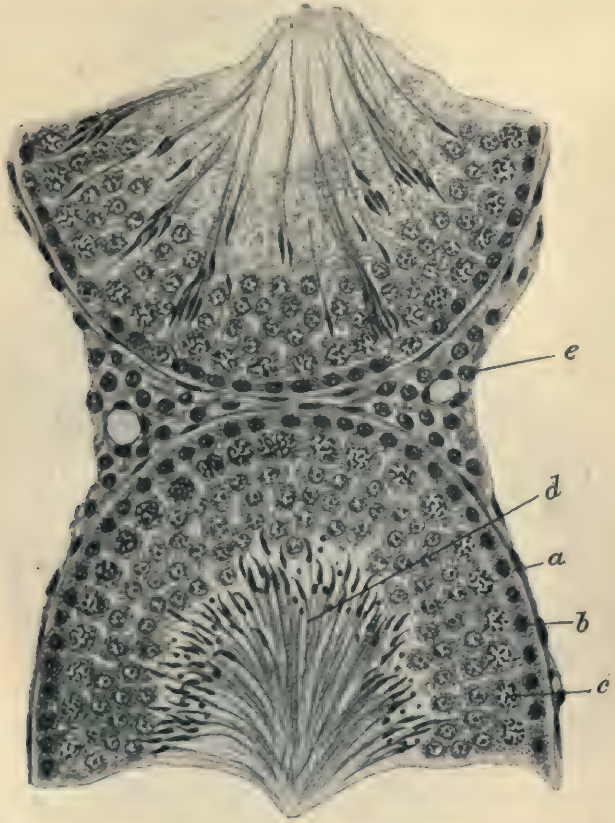

FIG. 48.—Section through portion of two seminiferous tubules in testis of rat.

a, Basement-membrane ; *b*, spermatogonium ; *c*, spermatocyte ; *d*, spermatozoa in cavity of tubule ; *e*, interstitial tissue containing vessels.

The spermatids, which in some seminiferous tubules lie on the inside of the spermatocytes, are the double products of division of the latter. The spermatids so formed may be seen as small cells with spherical nuclei, and forming irregular clumps on the inner surface of the tubule. Often, however, the spermatids are elongated, being partially converted into spermatozoa. As this process of transformation proceeds, the developing sperms become arranged in little groups. Associated with each group is a foot-cell, or a cell of Sertoli, which probably serves as a support and as a means of conveying nourishment to the growing spermatozoa.[1] The tails of the latter at this stage project freely into the cavity of the tubule, and a little later the spermatozoa shift bodily forward and become completely liberated. According to Loisel,[2] the orientation of the sperms in the testis is due to a secretion from the cells of Sertoli, together with certain of the other cells in the parietal layer of the seminiferous epithelium.

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[1] Curtis, "The Morphology of the Mammalian Seminiferous Tubule," *Amer. Jour. of Anat.*, vol. xxiv., 1918.

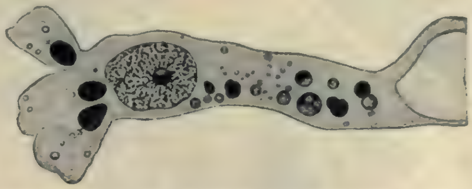

FIG. 49.—A cell of Sertoli with which the spermatids (three of which are shown) are beginning to be connected—human. (After Bramman, from Schafer.) The cell contains globules of nutritive substance, and similar smaller globules are seen in the spermatids.

In male animals which have a rutting season spermatogenesis occurs only at this time. At other seasons of the year the testes remain in a quiescent condition. The periodic activity of the testis is usually correlated with a great increase in the size of that organ (see pp. 22 and 55). In the hedgehog the interstitial cells have been shown to proliferate even more than the spermatogenetic tissue, the seminiferous tubules becoming widely separated.[3] The same fact has been observed in the woodchuck[4] after hibernation, and in the spring and summer. As with the hedgehog the interstitial hypertrophy is followed by regression with the approach of autumn.

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[1] Merkel, "Die Stützzellen des Menschlichen Hodens," *Müller's Archiv*, 1871. Brown, "On Spermatogenesis in the Rat," *Quar. Jour. Micr. Science*, vol. xxv., 1885. Bende, "Untersuchungen über den Bau und Funktioniren des Samenkanälchens einiger Säugethiere," *Arch. f. Mikr. Anat.*, vol. xxx., 1887.

[2] Loisel, "Facteurs de la Forme et de la Fasciculisation des Spermies dans les Testicules," *Jour. de l'Anat. et de la Phys.*, vol. xlii., 1906.

[3] Marshall, "The Male Generative Cycle in the Hedgehog," *Jour. of Physiol.*, vol. xliii., 1911. Similar changes occur in the mole. See Tandler and Gross, *Die Biologischen Grundlagen der Sekundären Geschlechtscharaktere*, Berlin, 1913.

[4] Rasmussen, "Seasonal Changes in the Interstitial Cells of the Testis in the Woodchuck," *Amer. Jour. of Anat.*, vol. xxii., 1917.

In some animals the renewal of activity in the testes is associated with the descent of these organs from their position in the abdominal cavity through the inguinal canal and into a cutaneous fold.[1] This

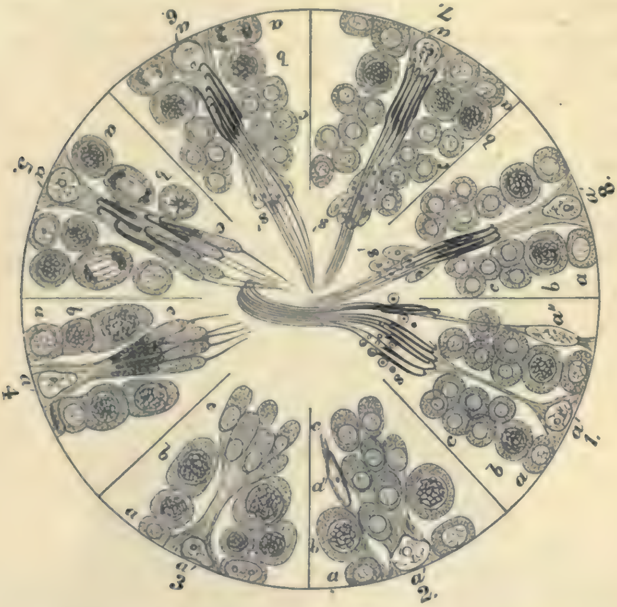

FIG. 50.—Diagram illustrating the cycle of phases in spermatogenesis. (From Schafer.)

a, Spermatogonia (seen dividing at 6) ; *a'*, *a''*, Sertoli cells ; *b*, spermatocytes (seen dividing at 5) ; *c*, spermatids ; *s'*, parts of spermatids which disappear when spermatozoa are fully formed ; *s*, seminal granules.

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[1] Berry Hart, "The Nature and Cause of the Physiological Descent of the Testes," *Jour. of Anat. and Phys.*, vol. xliv., 1910. The author sums up the essence of the process as follows : "The testis is united to a mammary area, at first by the testicular caudal ligament and the inguinal fold or gubernaculum. The developing gubernaculum, with the aid of the cremaster and peritoneum, forms a pit or fossa for the testis in the Rodentia ; a more complete canal or more or less pendulous scrotum in higher mammals. By subsequent disproportionate growth of canal and testes, and finally (according to Frank) by the involution and shrinkage of the gubernaculum, the testes in man become permanently lodged in the scrotum." Numerous references to literature are appended to this paper. When, as sometimes happens in man, one or both of the testes do not descend or only imperfectly descend, the condition is said to be one of cryptorchism. In cryptorchids spermatogenesis usually only takes place for a short time after puberty (one or two years), if at all, and then the seminiferous tissue degenerates, but the interstitial cells remain. Crew has suggested that the aspermatic state of such testicles is due to the greater temperature within the body as compared with the scrotum, and that the final stages of spermatogenesis are inhibited by the higher temperature ("A Suggestion as to the Aspermatic Condition, etc." *Jour. of Anat.*, vol. lxvi., 1922). Guyer has made another suggestion, based on his work with spermatotoxic sera

is transformed into the scrotum, which lies behind the penis (except in Marsupials, where it is in front). In many Mammals the descent takes place at an early age and is permanent. In others (most Rodents, Insectivores, and bats) the testes are withdrawn into the abdominal cavity after the breeding season is over. This is effected by the cremaster muscle. In Monotremes, Edentates, Cetacea, and Proboscidea there is no descent.[1]

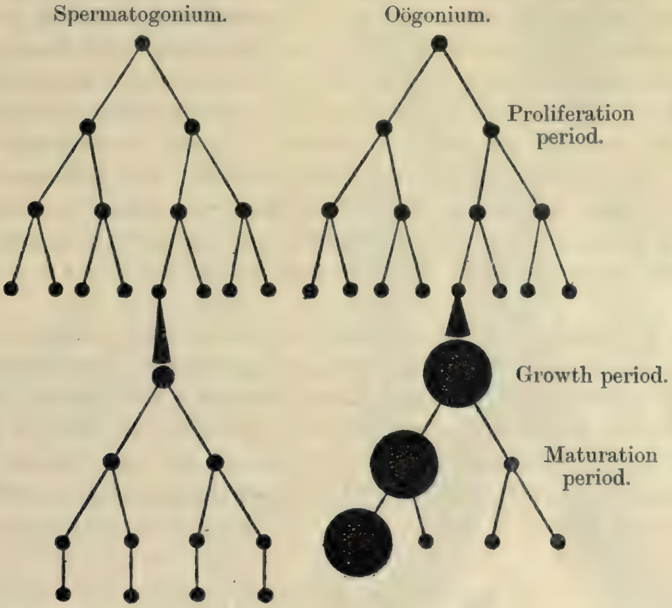

Fig. 51.—Scheme of spermatogenesis and oögenesis. (After Boveri.)

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prepared by repeatedly injecting fowls with sperms of rabbits; the sera are stated to be toxic for sperms of rabbits and guinea-pigs when injected into the blood at intervals for four or five weeks, partial or complete sterility resulting, the spermatogenetic tissue degenerating ("Studies on Cytolysins," III., *Jour. of Exp. Zool.*, vol. xxxv., 1922). Kuntz had found that after ligation of the vas deferens in the rat the seminiferous tissue degenerated in *both* testes, and it is suggested by Guyer that this result may have been due to spermatotoxins resulting from resorption (Kuntz, *Anat. Rec.*, vol. xvii., 1919). Kuntz's result is not confirmed by other observers, and Guyer's suggestion seems very unlikely on general grounds.

[1] Woodland has put forward a theory of the descent of the mammalian testes involving the inheritance of acquired characters. His view is that the descent has been caused by the action of mechanical strains resulting in rupture of the attachments, such strains being due to the inertia of the organs (which are larger than the ovaries of the female) reacting to the "impulsiveness" (*e.g.* leaping or galloping movements) involved in the activity of the animals (*Proc. Zool. Soc.*, 1903). Cunningham (J. T.), who adopts this view, points out that the descent takes place in the fœtus and is related to the general habits which begin soon after birth, and not to sexual habits (*Hormones and Heredity*, London, 1921).

The changes which occur in spermatogenesis may be summarised as follows: (1) A spermatogonium divides into two, one product of division passing into the second layer of the seminal epithelium and becoming a spermatocyte. (2) A primary spermatocyte, or mother-cell, divides, the number of chromosomes becoming reduced during this process to one-half the previous number. (3) A secondary spermatocyte so formed divides, giving rise to a spermatid. Subsequently the spermatid elongates, the nucleus becomes shifted to one end, and the spermatozoön which is formed in this way is set free. The process is continually going on in the seminiferous tubules of the testis, successive crops of spermatozoa being from time to time produced. The various stages of development may generally be observed in the same testis, or even within the limits of a single tubule.[1]

It is supposed that the reduction in the number of the chromosomes is a preparation of the conjugating cells for their subsequent union in fertilisation, and is a means by which this number is held constant in the species (see p. 126).[2] In those animals in which reproduction is normally effected without the intervention of a spermatozoön (parthenogenesis) the ovum may discharge only one polar body instead of two.

Structure of Spermatozoa

A fully developed human spermatozoön consists of a flattened egg-shaped head, a short cylindrical body or middle-piece, and a long delicate vibratile tail. Lying anterior to the head is a small apical body, or achrosome, which in some animals bears a little barb-like projection by means of which the spermatozoön bores its way into the ovum. The tail of the sperm consists of an axial filament surrounded by a protoplasmic envelope, which becomes very thin or disappears altogether at the extremity, leaving a short naked end-piece. The axial filament passes anteriorly through the middle-piece, and ends in a small knob (the end-knob) at the base of the head.

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[1] The process of reduction may result in two sorts of spermatozoa being produced, these after fertilisation giving rise respectively to the two sexes, in whose body cells the chromosomes may differ in number or in kind; that is to say, one sex may carry two chromosomes specially associated with sex and called the "X chromosomes," while the other sex only carries one X chromosome, with or without another smaller chromosome called the "Y chromosome" (see Chapter XV. below).

[2] For an account of the process of spermatogenesis in different animals and plants, and a discussion of the phenomena described, see Wilson (E. B.), *The Cell in Development and Inheritance*, 2nd Edition, London, 1900. In this work the theories of Weismann and others are dealt with, and a full account of the literature is given up to 1900. For later work see Doncaster, *An Introduction to the Study of Cytology*, Cambridge, 1920.

Ballowitz[1] has shown that the axial filament is composed of a number of parallel fibrillæ, like a muscular fibre.

Schweigger-Seidel[2] and La Valette St. George[3] were the first to prove, independently but almost simultaneously, that the spermatozoön has the essential characteristics of a complete cell. The head contains the nuclear material, which is surrounded by a thin layer of cytoplasm. The end-knob is said to represent the centrosome.

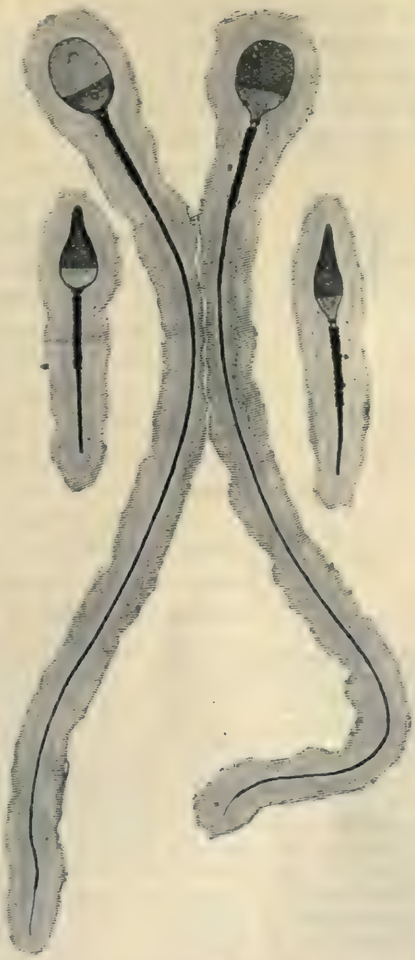

Fig. 52.—Human spermatozoa on the flat and in profile. (After Bramman, from Schafer.) × 2500. Those on the right have adhering protoplasm. The tail is only partly shown in the two seen in profile.

Spermatozoa, conforming with more or less closeness to the type described above, occur in the great majority of multicellular animals from the Cœlenterata up to Mammals. In Pisces, and also in Echinoderms, the general resemblance is very distinct, but in other forms of life there is more diversity in the shape assumed by the spermatozoa. "The head (nucleus) may be spherical, lance-shaped, rod-shaped, spirally twisted, hook-shaped, hood-shaped, or drawn out into a long filament; and it is often divided into an anterior or a posterior piece of different staining capacity, as is the case with many birds and Mammals. The achrosome sometimes appears to be wanting, *e.g.* in some fishes. When present, it is sometimes a minute rounded knob, sometimes a sharp stylet, and in some cases terminates in a sharp barb-spur by which the spermatozoön appears to penetrate the ovum (*Triton*)."[1] The middle-piece also shows considerable variability. It may be spherical, cylindrical, or flattened against the nucleus; sometimes it is of great length, and sometimes it passes insensibly into the flagellum or tail. The latter, in some insects and fishes, gives attachment to a membranous fin. The end of the axial filament, as already mentioned, is sometimes left naked, giving rise to the end-piece.

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[1] Ballowitz, "Untersuchungen über die Struktur der Spermatozoen," *Arch. f. Mikr. Anat.*, vol. xxxii., 1888, and vol. xxxvi., 1890; *Zeitsch. f. wiss. Zool.*, vol. lx., 1890, and vol. lxii., 1891.

[2] Schweigger-Seidel, "Über die Samenkörperchen und ihre Entwickelung," *Arch. f. Mikr. Anat.*, vol. i., 1865.

[3] La Valette St. George, "Über die Genese der Samenkörper," *Arch. f. Mikr. Anat.*, vol. i., 1865.

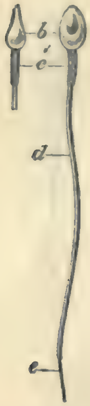

Fig. 53.

Human spermatozoa (× 1000). (After Retzius, from Schafer.)

1, In profile; 2, view on the flat; *b*, head; *c*, middle-piece; *d*, tail; *e*, end-piece of tail, described as a distinct part by Retzius.

The tadpole-like shape is not an essential characteristic of the spermatozoön, for in certain Arthropods and Nematodes there is no flagellum, and the sperms are consequently incapable of spontaneous movement. In the daphnid *Polyphemus* the sperms are said to be amœboid. In some crustacean spermatozoa there are a number of radiating spine-like processes which seem to take the place of the flagellum.

In other animals, and notably in the gasteropod mollusc *Paludina*, there are two kinds of spermatozoa. In this animal one is of the usual type, whereas the other is larger and worm-shaped, with a tuft of cilia at one end. The smaller variety alone is said to be functional.[2]

The size of the sperm varies greatly in different animals. In man its length is about ·05 millimetre or a 300th of an inch, the head and the middle-piece being each about ·005 millimetre long.

It is obvious that the sperm contributes comparatively little material to the fertilised ovum, being provided with only sufficient protoplasmic substance to form a locomotive apparatus by means of which it gains access to the ovum. The predominantly destructive metabolism of the spermatozoön as contrasted with the ovum has been strongly emphasised by Geddes and Thomson,[1] who believe it to exemplify those katabolic phenomena which, according to their view, are usually associated with the male sex.

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[1] Wilson, *loc. cit.*

[2] For further details of the structure of various kinds of sperms see Wilson, *loc. cit.*; also Ballowitz's papers just referred to, and Retzius' *Biologische Untersuchungen*, vols. xi., xii., and xiii., Stockholm and Jena. The latter contains numerous large plates with figures of spermatozoa. For sexual differences in sperms (numbers of chromosomes, etc.), see Chapter XIII. See also von Winiwarter, *Arch. de Biol.*, vol. xxvii., 1912 (man); Wodsedalek, *Biol. Bull.*, vol. xxv., 1913 (pig); vol. xxvii., 1914 (horse); Leplat, *Arch. de Biol.*, vol. xxv., 1910 (cat); Painter, *Jour. Exp. Zool.*, vol. xxxv., 1922 (opossum); Guyer, *Biol. Bull.*, vol. xxi., 1916 (fowl); and Swift, *Amer. Jour. of Anat.*, vol. xx., 1916 (fowl). See also references on p. 128 above.

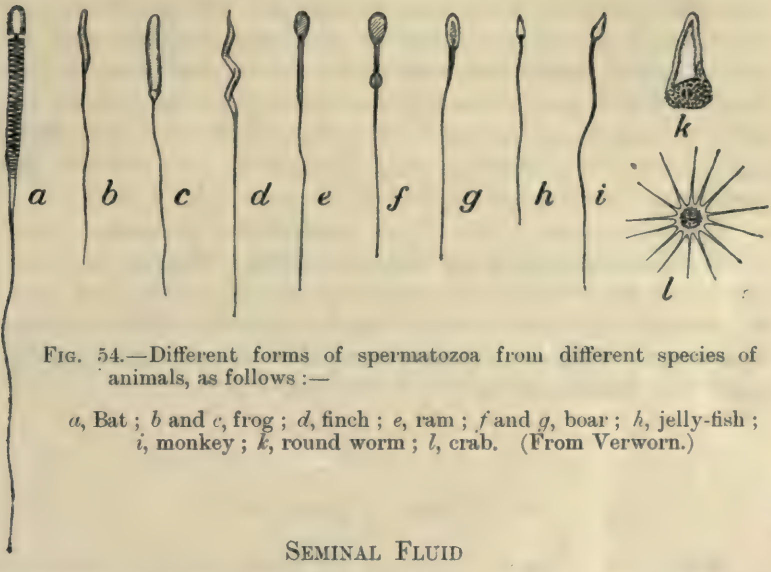

FIG. 54.—Different forms of spermatozoa from different species of animals, as follows:—

a, Bat; *b* and *c*, frog; *d*, finch; *e*, ram; *f* and *g*, boar; *h*, jelly-fish; *i*, monkey; *k*, round worm; *l*, crab. (From Verworn.)

SEMINAL FLUID

The semen serves as the mechanical medium in which the spermatozoa move. It is possible also that it has a nutritive function. It is secreted by the seminiferous tubules. It is milky in appearance, and has a characteristic smell. When ejected the seminal fluid is mixed with the secretions of the accessory glands (prostate, etc.), which render it still more milky. On standing it tends to become gelatinous. According to Lode,[2] the specific gravity of semen is between 1·027 and 1·046.

The number of spermatozoa which exist in normal human semen is subject to much variation. Lode[3] has shown that it diminishes almost to zero after a number of successive emissions, but increases again after an interval of several days. The average number is given as 60,000 per cubic centimetre. The number of sperms present in the ejected seminal fluid of the dog was also found to be greater at the end of an interval in which there were no emissions, but it did not continue to increase after more than eight or ten days. In a normal emission of semen (man) Lode calculates that there are about 226,000,000 spermatozoa, but that the number may vary from zero to 551,000,000.

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[1] Geddes and Thomson, *The Evolution of Sex*, Revised Edition, London, 1901.

[2] Lode, "Untersuchungen über die Zahlen- und Regenerationsverhältnisse der Spermatozoiden bei Hund und Mensch," *Pflüger's Arch.*, vol. l., 1891.

[3] Lode calculates that about 339,385,500,000 spermatozoa must be produced in man between the ages of twenty-five and fifty-five.

Lloyd-Jones and Hays[1] have investigated the effects of excessive sexual activity upon the semen and offspring of rabbits. They found that the semen becomes less viscous and the spermatozoa less numerous while their motility is somewhat reduced also. The percentage of pregnancies induced by the services becomes less as the number of previous services increases, but the sizes of litters actually born do not appear to be reduced until after the fifteenth copulation. The offspring themselves were not affected, except possibly in regard to sex (see below, Chapter XIV., p. 637).

The spermatozoa which are not ejaculated degenerate. The tails break off, and undergo a gradual liquefaction. The end products are ultimately absorbed by the epithelial cells of the seminal vesicles, and perhaps by the cells of the vasa deferentia or of the testis itself. According to Perez,[2] the spermatozoa of male newts which are kept apart from females are absorbed by phagocytes.[3]

MOVEMENTS OF SPERMATOZOA

When the spermatozoa are in the testis they are inactive, but they begin to move rapidly as soon as they are ejected in the seminal fluid. The rate at which they progress has been estimated at 3·6 millimetres per minute.[4] Bischoff[5] found spermatozoa at the top of the oviduct in the rabbit nine or ten hours after coition.

It is probable that the ejected spermatozoa continue to undergo movement, as a general rule, so long as they retain their vitality, the rate of movement becoming gradually diminished and ceasing altogether shortly before death. In bats, however, during the period of hibernation the sperms become quiescent without dying, their vigour being restored in the spring when they conjugate with the ova.[6] It is exceedingly probable also that in the spotted viviparous salamander and the other animals referred to below

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[1] Lloyd-Jones and Hays, "The Influence of Excessive Sexual Activity of Male Rabbits," I. and II., *Jour. of Exp. Zool.*, vol. xxv., 1918. *Cf.* Amantea, "Recherches sur la Sécrétion Spermatique," *Arch. Ital. de Biol.*, vols. lxii. to lxiv., 1914-16.

[2] Perez, "Résorption phagocytaire des Spermatozoïdes," *Proces-Verbaux de la Soc. des Sciences de Bordeaux*, 1904.

[3] For chemistry of the spermatozoön and semen, see Chapter VIII.

[4] Lott, *Anatomie und Physiologie des Cervix Uteri*, Erlangen, 1871. According to Adolphi ("Ueber das Verhalten von Schlungenspermien in strömender Flussigkeiten," *Anat. Anz.*, vol. xxix., 1906), the spermatozoa of the adder swim at the rate of 50 μ to 80 μ per second.

[5] Bischoff, *Die Entwickelung des Kaninchen-Eies*, Giessen, 1842.

[6] See p. 131.

(p. 178), in which the male cells retain their vitality for long periods, these must at such times remain quiescent, for otherwise their store of energy would soon become exhausted.

The spermatozoa swim by means of their tails. The movement is represented in the accompanying figure (taken from Nagel),[1] which shows the successive positions assumed by the sperm in a state of locomotion. A wave of movement first makes its appearance in the forepart of the tail, and then rapidly travels backwards to the end, to be succeeded by a fresh wave which follows the same course. It would seem that the driving force is located a little behind the head. The head itself does not appear to be concerned in the movements of locomotion.

The movements of spermatozoa have probably been studied most closely in Insecta and Echinodermata. Buller[2] says that the sperms of the Echinoidea in a drop of sea-water (or the medium in which they are normally discharged) swim spirally, so long as they do not come into contact with the surface. The spirals may be so steep that the sperms appear to move almost in a straight line, in which case progression across the field of the microscope is relatively rapid. In other cases the incline of the spiral is so slight that the spermatozoa swim almost in circles, and consequently move forward across the microscopic field with great slowness. Every gradation between these two extremes was observed, but the more active sperms generally swam in the steeper spirals.

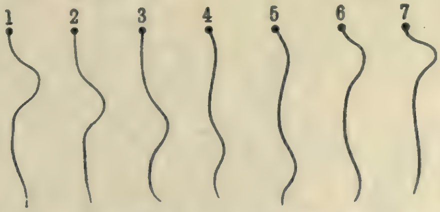

Fig. 55.—Diagram illustrating wave-like movement of swimming spermatozoön. (From Nagel.)

Dewitz[3] has shown that when the spermatozoa of the cockroach are put into 0·6 per cent. solution of sodium chloride, and placed between two surfaces, such as those of a slide and a cover-glass, they collect after a short time, partly upon the upper surface of the slide and partly upon the lower surface of the cover-glass. In these positions they describe circles with their tails, the rotation being invariably counter-clockwise. The bulk of the liquid remains free from spermatozoa, the latter adhering to the glass surfaces after having once reached them. If a ball be placed in the fluid, its surface is soon sought by the spermatozoa.[1] Verworn has described this phenomenon under the name of "barotaxis," and states that it is caused by pressure acting unequally on different sides of the spermatozoön. It is said to be of great importance in the process of fertilisation, and probably assists the spermatozoön in entering the micropyle of the ovum.[2] Dewitz's observations were subsequently confirmed by Ballowitz.[3]

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[1] Nagel, *Handbuch der Physiologie des Menschen*, vol. ii., Braunschweig, 1906.

[2] Buller, "Is Chemotaxis a Factor in the Fertilisation of the Eggs of Animals?" *Quar. Jour. Micr. Science*, vol. xlvi., 1902.

[3] Dewitz, "Ueber Gesetzmässigkeit in der Ortsveränderung der Spermatozoen, etc.," *Pflüger's Archiv*, vol. xxxviii., 1886. Rotation by spermatozoa seems to have been recorded first by Eimer, "Untersuchungen über den Bau und die Bewegung der Samenfäden," *Verhand. d. Phys. Med. Gesel. zur Würzburg*, vol. vi., 1874.

Counter-clockwise rotation upon surfaces was first recorded for the spermatozoa of Echinoderms by Dungern,[4] who discovered the phenomenon in *Sphærechinus* and *Arbacia*. About the same time Buller,[5] who has described the manner of rotation more fully, observed its occurrence in the sperms of various other Echinoderms, and particularly in those of *Echinus*: "When a spermatozoön comes in contact with a glass surface, unless it becomes immediately fixed to the glass [it] begins to make characteristic circular revolutions upon it. If the cover-glass be supported by pieces of another cover-glass, and the upper surface of the drop in contact with it be carefully focused, it is seen that all the spermatozoa which are not attached by their heads, but are moving there, are revolving from the observer's point of view in clockwise direction. If the lower surface of the drop in contact with the slide be examined, a reverse rotation —the counter-clockwise—is seen to be the rule. In both cases, therefore, if the surfaces be regarded from the point of view of the spermatozoa, the rotation is always in one direction—namely, the counter-clockwise."

The head is the only visible part of the rotating spermatozoön. This moves rapidly round in a circle, which in the case of *Echinus* is slightly less than 0·05 millimetre (or the length of a spermatozoön) in diameter. A normally rotating sperm of *Sphærechinus* was observed to make 109 circles around one point in ninety seconds. The rate of movement of the head is calculated to be about 0·12 millimetre per second, or 7·2 millimetres per minute.

The characteristic rotation may likewise take place upon surfaces which are bounded by air (instead of glass), and it has been observed also upon the outer surface of the gelatinous layer of the ova of *Echinus*. Buller concludes, therefore, that the nature of the surface is not an important factor in the process.

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[1] Ballowitz, "Untersuchungen über die Struktur der Spermatozoen, etc.," *Zeitsch. f. Zool.*, vol. i., 1890.

[2] Verworn, *General Physiology*, Lee's Translation from the second German Edition, London, 1899.

[3] Ballowitz, *loc. cit.*

[4] Dungern, "Die Ursachen der Specietät bei der Befruchtung," *Zentralbl. f. Physiol.*, vol. xv., 1901.

[5] Buller, *loc. cit.*

Ballowitz expresses the opinion that the circles described by insects' sperms are simply the modified spirals made by the free-swimming cells. Buller thinks that this view, which provides a purely mechanical explanation, is also probably correct for the spermatozoa of Echinoderms.

Since counter-clockwise rotation upon surfaces has been observed in the spermatozoa of two groups as widely separate as the Insecta and the Echinodermata, it would seem probable, as Buller remarks, that it will be found to occur in other animals.

The spermatozoa of Mammals, in traversing the female passages after copulation, make their way upward towards the ovaries in opposition to downward currents set up by the cilia of the lining epithelia. Kraft[1] has shown that when rabbits' spermatozoa, in a state of feeble motion, are placed upon the inner wall of the oviduct their movements become more vigorous and they swim against the current which the cilia produce. Roth[2] also has succeeded in experimentally illustrating the same fact.

It is commonly stated that in man the passage of the spermatozoa from the vagina inwards is assisted by a contraction of the muscular wall of the uterus, which compresses the cavity of that organ into which the sperms are drawn when relaxation takes place.[3] The contraction of the uterus is said to be a reflex action resulting from copulation. It has also been suggested that, during copulation, a mucous plug which is ordinarily contained in the cervix may be temporarily and partially expelled into the vagina and afterwards withdrawn with the spermatozoa adhering to it.[4]

So also Heape[5] has shown that in the rabbit the passage of the spermatozoa into the uterus is probably assisted by a sucking action on the part of the latter organ. The os uteri, which is situated above the ventral wall of the vagina, was observed to dip down into the seminal fluid at the bottom of the vagina, and then to be withdrawn again in conjunction with a peristaltic contraction of the uterus. These movements were repeated at intervals. Moreover, it was found that the sucking action could be induced artificially by stimulating the erectile tissue of the vulva. It is probable, however, that the spermatozoa, after once entering the uterus, proceed to their destination unassisted, and that the direction of their movement is determined by the capacity they possess to respond to the stimuli set up by opposing currents. Moreover, pregnancy has been known to follow imperfect coition in man, so that there can be no doubt that under certain circumstances the spermatozoa are capable of passing inward by their own unaided efforts.[1]

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[1] Kraft, "Zur Physiologie des Flimmerepithels bei Wirbelthieren," *Pflüger's Archiv*, vol. xlvii., 1890.

[2] Roth, "Ueber das Verhalten beweglicher Mikroorganismen in strömender Flüssigkeit," *Deutsche med. Wochenschrift*, vol. xix., 1893. Verworn (*loc. cit.*) describes this property of spermatozoa under the name of rheotaxis, which, he says, is a special kind of barotaxis. See also Adolphi, "Die Spermatozoen der Säugethiere schwimmen gegen den Strom," *Anat. Anz.*, vol. xxvi., 1905.

[3] See Beck, "How do the Spermatozoa enter the Uterus?" *Amer. Jour. of Obstet.*, vol. viii., 1875.

[4] See Williams, *Obstetrics*, New York, 1904.

[5] Heape, "The Artificial Insemination of Mares," *Veterinarian*, 1898.

INSEMINATION

The act of copulation results in the introduction of seminal fluid through the generative aperture of the female. The mechanism by which this is effected in the higher animals is described in a future chapter, where the functions of the accessory male organs are dealt with. The introduction of the fluid into the female generative passages is known as insemination (as distinguished from impregnation, which is the term used in reference to the female when fertilisation takes place[2]).

It is obvious that in those animals which ovulate spontaneously during the œstrus periods it should be possible to induce pregnancy at such times by the artificial introduction of spermatozoa into the vagina or into the uterus. That this could actually be effected was probably first demonstrated by Spallanzani,[3] though there is evidence that the practice of artificial insemination was not unknown to the Arabs many centuries ago.[4] The following is a description of Spallanzani's original experiment, as quoted from a contemporary English translation :—

"I chose a bitch spaniel of moderate size which had before had whelps. Suspecting, from certain appearances, that she would soon be in heat, I confined her in an apartment, where she continued a long time, as will be seen below. For greater security, that she might never be let loose, I fed her myself, and kept the key the whole time. On the thirteenth day she began to show evident signs of being in heat; the external parts of generation were tumid, and a thin stream of blood flowed from them. On the twenty-third day she seemed fit for the admission of the male, and I attempted to fecundate her artificially in the following manner. A young dog of the same breed furnished me, by a spontaneous emission, with nineteen grains of seed, which were immediately injected into the matrix, by means of a small syringe introduced into the vagina. As the natural heat of the seed of animals of warm blood may be a condition necessary to render fecundation efficacious, I had taken care to give the syringe the degree of heat which man and dogs are found to possess, which is about 30° [or between 99° and 100° F.]. Two days after the injection, the bitch went off her heat, and in twenty days her belly appeared swollen, which induced me to set her at liberty on the twenty-sixth. Meanwhile the swelling of the belly increased; and sixty-two days after the injection of the seed, the bitch brought forth three lively whelps, two male and one female, resembling in colour and shape not the bitch only, but the dog also from which the seed had been taken. Thus did I succeed in fecundating this quadruped; and I can truly say, that I never received greater pleasure upon any occasion, since I first cultivated experimental philosophy."

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[1] For further information regarding the passage and fate of the spermatozoa in the female body, see Kohlbrugge, "Die Verbreitung der Spermatozoviden im Weiblichen Körper, etc.," *Arch. f. Entwick.*, vol. xxxv., 1912.

[2] That is to say, the animal is inseminated when the spermatozoa are introduced, and it is impregnated when the ovum becomes fertilised by a sperm. See Heape, "The Artificial Insemination of Mammals," *Proc. Roy. Soc.*, vol. lxi., 1897.

[3] Spallanzani, *Dissertations*, vol. ii., London, 1784.

[4] Gautier, *Le Fécondation artificielle, etc.*, Paris, 1889.

Spallanzani also records a similar experiment by Pierre Rossi, in which a dog was impregnated by artificial means.

Considerable success has been obtained in recent years in experiments on the artificial insemination of dogs. Gautier[1] refers to a case in which pregnancy was induced by this means. Albrecht[2] and Plönnis[3] have also described experiments in which they successfully inseminated dogs by artificial methods (see p. 649). Heape[4] has recorded a series of experiments carried out by Sir Everett Millais on the artificial insemination of Basset hounds. The present writer has succeeded in inducing pregnancy by this method in a Dandie Dinmont terrier. Moreover, there are numerous cases on record in which dogs have been successfully inseminated artificially as a means of overcoming certain forms of barrenness (see p. 649). The method adopted in all these experiments was substantially the same as that employed by Spallanzani.

Artificial insemination is now also practised on mares, donkeys, and cows, and usually with the object of remedying sterility. In thoroughbred mares especially it has proved of great service, having been the means of preserving for breeding purposes many valuable animals which otherwise would have been discarded.[1]

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[1] Gautier, *loc. cit.*

[2] Albrecht, "Künstliche Befruchtung," *Wochenschr. f. Thierheilkunde und Viehzucht*, Jahrg. xxxix.

[3] Plönnis, "Künstliche Befruchtung einer Hünden, etc.," *Inaug. Dissert.*, Rostock, 1876.

[4] Heape, *loc. cit.*

Iwanoff[2] has described experiments in which pregnancy was induced in rabbits and guinea-pigs by the artificial injection of testicular fluid into the female generative passages. The same investigator states that he induced hybridisation between a male rat and a female mouse by artificially inseminating the latter (see p. 649, Chapter XIV.).

He has shown, further, that the spermatozoa retain their vitality sufficiently long to admit of their being employed successfully in artificial insemination if they are kept in solutions of various salts (sodium chloride, sodium carbonate, etc.) or in serum instead of in the secretions of the accessory generative glands. Hunter appears to have been the first to practise artificial insemination upon a woman (previously sterile),[3] but it has since been successfully adopted by various medical men, the method being to inject the spermatozoa through the os into the cavity of the uterus (see p. 647).

With those animals whose ova are normally fertilised outside the body, artificial insemination is a still simpler process. Spallanzani was the first to show that the eggs of various species of Amphibia could be fertilised by the application of fluid obtained from the testes or seminal vesicles of the male, and that the frogs and newts which were generated by this means in no way differed from those produced in nature. Spallanzani was also successful in artificially fecundating the eggs of the silk-worm moth.

Artificial impregnation of fish ova was first employed by Jacobi,[4] and the method which he adopted is practically the same as that habitually practised at the present day for stocking water-courses with fish.

The vitality of the spermatozoön appears to vary widely in the different species of animals.

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[1] For references to particular experiments see Heape, "The Artificial Insemination of Mares," *Veterinarian*, 1898; also a booklet published by Huish (*The Cause and Remedy of Sterility in Mares, Cows, and Bitches*, London, 4th Edition, 1899), in which a large number of cases are described in which artificial insemination was successfully carried out; also Iwanoff, "De la Fécondation Artificielle chez les Mammifères," *Arch. des Sciences Biologiques*, vol. xii., 1907. The last-mentioned paper contains an account of a very large series of experiments on horses, cows, and sheep, with a full description of the practical methods employed, and a very complete account of the literature of the subject,

[2] Iwanoff, "La Fonction des Vésicules séminales, etc.," *Jour. de Phys. et de Path. gen.*, vol. ii., 1900.

[3] See Home, "An Account of the Dissection of an Hermaphrodite Dog," *Phil. Trans.*, 1799.

[4] See Günther, *Introduction to the Study of Fishes*, Edinburgh, 1880.

Leeuwenhoek,[1] and subsequently Prévost and Dumas,[1] state that they found moving sperms in the internal genital organs of female rabbits and dogs eight days after coition. Bonnet[2] says that he observed motionless sperms, which, therefore, were probably dead, but had not yet undergone disintegration, in a bitch seventeen and a half days after coition. In a series of experiments upon the longevity of the spermatozoön in the rabbit, it was found that these cells can survive in the vasa deferentia for at least ten days after the removal of the testes, but that they die before the end of thirteen days.[3]

Spallanzani[4] stated that a hen can lay fertilised eggs twenty days after impregnation, but it would appear that there is some variation. Elford[5] states that a drop in the fertility of the eggs takes place on the ninth day, that 50 per cent. of the eggs are fertile on the tenth day, 16 per cent. on the fifteenth, and after that none at all. Philips[6] and Kaupp[7] have made confirmatory observations. The first fertile egg in fowls is said to be laid three or four days after mating. In the turkey one insemination is sufficient to fertilise a whole batch of eggs. Riddle[8] found the sperms of the ring-dove retained their fertilising power for nearly eight days.

Strassmann[9] has recorded a case in which human spermatozoa survived in the female generative passages for a week after coition. Bossi[10] refers to a similar instance where the sperms lived for over twelve days. In another case described by Dührssen,[11] living spermatozoa were found in a woman who stated that coition had not been experienced for three and a half weeks.

In many species of bats, as already mentioned, copulation takes place in autumn and ovulation in the following spring, so that the spermatozoa retain their vitality while stored up in the uterus during the hibernating period. Sperms obtained from the females at this time are dormant, but regain their vitality on the application of warmth.[1]

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[1] See Waldeyer's article in Hertwig's *Handbuch der Entwicklungslehre*, Jena, 1903.

[2] Bonnet, "Giebt es bei Wirbelthieren Parthenogenesis," *Merkel und Bonnet's Ergebnisse d. Anat. u. Entwick.*, vol. ix., 1900.

[3] Marshall and Jolly, "Contributions to the Physiology of Mammalian Reproduction: The Œstrous Cycle in the Dog," *Phil. Trans.*, B., vol. cxcviii., 1905.

[4] Spallanzani, *loc. cit.*

[5] Elford, *Canada Exp. Farms Report*, 1916.

[6] Philips, *Jour. Amer. Assoc. Instr. and Invest. Poultry Husbandry*, 1918.

[7] Kaupp, *North Canadian Exp. Stat. Bull.*, 1915.

[8] Riddle and Behre, "Studies on the Physiology of Reproduction in Birds: IX. On the Relation of Stale Sperm to Fertility and Sex in Ring-doves," *Amer. Jour. of Physiol.*, vol. lvii., 1921.

[9] Strassmann, *Lehrbuch der gerichtlichen Medizin*, 1895.

[10] Bossi, "Étude Clinique et Expérimentale de l'Époque la plus favorable à la Fécondation de la Femme," *Rivista di Obstet. e Ginecol.*, 1891.

[11] Dührssen, "Lebendige Spermatozoen in der Tube," *Centralbl. f. Gynäk.*, 1893.

The spermatozoa of some warm-blooded animals will stand considerable variation in temperature and still retain their vitality. Thus they have been known to live for many hours at ordinary room temperature; but cold, while it reduces their motility, tends to prolong their life, the motility being regained under a higher temperature. Heape states that some seminal fluid of a dog was sent to him by post in a glass tube, and on being examined eighteen hours after it was obtained, fully half the spermatozoa were found to be active and vigorous, while increased warmth stimulated to activity those which showed signs of sluggishness but did not revive the remainder.

Chelchowski,[2] in describing the methods adopted in the artificial insemination of mares, lays stress upon the necessity of keeping the seminal fluid warm, and states that, if this is done, it is possible to keep the sperms alive for twenty hours; but it is possible that Chelchowski may have mistaken absence of movement under a low temperature for death.

The experimental work of Wolf and of other recent investigators is described below in the chapter on fertility (p. 650).

The case of bats, which has been referred to above, has a parallel in certain cold-blooded animals. Thus, according to Rollinat,[3] in snakes belonging to the species *Tropidonotus viperinus* the females are usually inseminated in the autumn, whereas the eggs are not laid until the beginning of the following summer. Also in the case of the spotted viviparous salamander (*Salamander maculosa*), after the birth of the young, which occurs about the month of May, a new batch of ova pass into the oviducts and are fertilised (prior to the commencement of the sexual season) by spermatozoa which were introduced in the July of the previous year, and thereafter stored in the uterus.[4] It is obvious that in both these cases the spermatozoa retain their vitality in the female for periods of many months.

In animals like the earthworm, in which the spermatozoa are stored in special reservoirs known as spermathecæ, it is probable that they retain their vitality for long periods. Lang[5] has shown

[1] See Eimer and other references given on p. 131.

[2] Chelchowski, *Die Sterilität des Pferdes*, Wien, 1894. See also Lewis, "The Vitality of Reproductive Cells," *Bull. 96, Agric. Exper. Stat., Oklahoma*, 1911.

[3] Rollinat, "Sur l'Accouplement des Ophidiens a la Fin de l'Eté et au Commencement de l'Automne," *Bull. Zool. Soc. France*, vol. xxiii., 1898.

[4] Sedgwick, *Student's Text-Book of Zoology*, vol. ii., London, 1905.

[5] Lang, "Über Vorversuche zu Untersuchungen über die Varietätenbildungen von *Helix hortensis* Müller and *Helix nemoralis* L.," *Festschr. zum siebzigsten Geburtstage von Ernst Haeckel*, Jena, 1904.

that the sperms may live for three years in the vesiculæ seminales of snails.

The extreme longevity possessed by the male cells of some insects is still more remarkable. Von Siebold[1] states that the spermatozoa of bees may survive for four or five years. Moreover, queen ants have been known to lay fertile ova thirteen years after the last intercourse with a male.

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[1] Von Siebold, "Fernere Beobachtungen über die Spermatozoen Wirbelloser Tiere," *Müller's Archiv*, 1837.

CHAPTER VI

FERTILISATION [1]

> "Although it be a known thing subscribed by all, that the fœtus assumes its origin and birth from the male and female, and consequently that the egge is produced by the cock and henne, and the chicken out of the egge, yet neither the schools of physicians nor Aristotle's discerning brain have disclosed the manner how the cock and its seed doth mint and coine the chicken out of the egge."—HARVEY.

ALTHOUGH much progress has been effected, and many new facts have been discovered, since Harvey wrote his famous dissertation on "The Efficient Cause of the Chicken," the actual nature of the process whereby the ovum, after being discharged from the ovary, is endowed with a new vitality through union with a spermatozoön, is a problem the solution of which is still far from complete.

In 1843 Martin Barry,[2] as already mentioned, first observed the union of the spermatozoön and ovum in the rabbit, and a little later Newport[3] recorded its occurrence in the frog; but it was not until the last quarter of the nineteenth century that the significance of the process was realised. It was largely through the work of Hertwig, Strasburger, and van Beneden that most biologists came to believe that the union of the nuclei of the gametes was the essential act in the process of conjugation. The more recent investigations of Boveri and others do not, however, entirely support this conclusion.

As already described, the head of the spermatozoön represents the nucleus, and contains the chromatin material. When the sperm penetrates into the substance of the ovum the tail becomes absorbed, but the head remains as the male pronucleus. The matured nucleus of the ovum, or female pronucleus (the two polar bodies having been discharged), passes towards the centre of the cell, where it unites with the male pronucleus which generally becomes somewhat enlarged. The middle-piece of the spermatozoön also enters the egg,

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[1] Revised, with numerous additions, by Cresswell Shearer.

[2] Barry, "Spermatozoa Observed within the Mammiferous Ovum," *Phil. Trans.*, 1843.

[3] Newport, "On the Impregnation of the Ovum in the Amphibia," *Phil. Trans.*, 1851.

and, according to Boveri,[1] induces the formation of a centrosome, which, after the completion of fertilisation, initiates the process of cell division. Cytoplasmic filaments arrange themselves around the centrosome in the form of a star, the sperm-aster, which accompanies the male pronucleus, and afterwards comes to lie alongside of the segmentation nucleus (as the nucleus formed by the union of the two pronuclei is called). In the segmentation nucleus the normal number of chromosomes characteristic of the species is once more restored. The oösperm, or zygote, produced in this way is the starting-point of a long series of cell divisions which culminate in the formation of a new, completely developed individual.

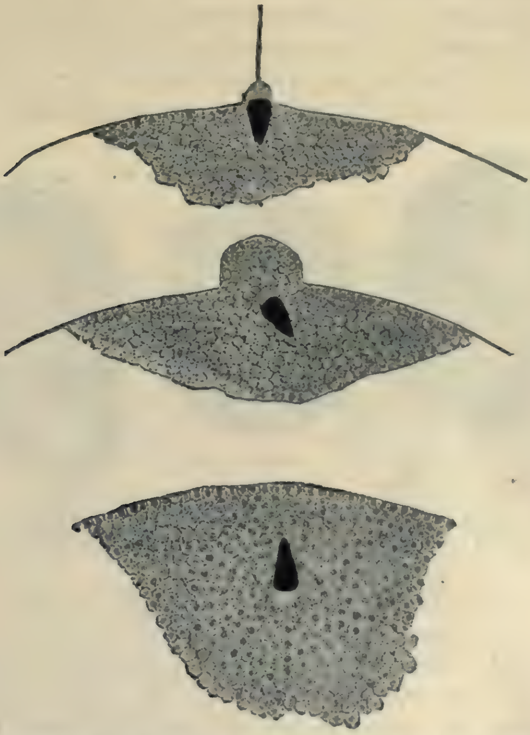

Fig. 56. — Successive stages in the fertilisation of an ovum of *Echinus esculentus*, showing the entrance of the spermatozoön. (From Bryce.)

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[1] Boveri, *Zellen Studien IV.*, *Ueber die Natur der Centrosomen*, Jena, 1901. Jenkinson, "Observations on the Maturation and Fertilisation of the Egg of the Axolotl," *Quar. Jour. Micr. Science*, vol. xlviii., 1904, has recently stated that the middle-piece of the spermatozoön, after forming the centre of the sperm-sphere and sperm-aster, completely disappears, and that the centrosome is formed from the sperm-nucleus at a later stage. (The sperm-sphere is the clear area which forms in the ovum round the head and middle-piece of the spermatozoön shortly after its entrance.)

Jenkinson, who has carried out a series of experiments intended to elucidate the physical processes occurring in fertilisation, draws the conclusion that the structures which appear in the ovum are produced under the influence of the middle-piece and centrosome. He supposes these bodies to possess the power of withdrawing water from the cytoplasm, of swelling up and dissolving in the water so absorbed, and then giving off radial outgrowths which precipitate the proteins of the cell, and so produce the fertilisation spindle. Jenkinson lays some stress on the fact that a watery fluid collects in vacuoles in the centre of the sperm-sphere of the axolotl, and regards the presence of this fluid as evidence that the sperm introduces a hydroscopic substance into the ovum. In confirmation of this the experiments show that a hydroscopic particle is capable of giving rise to an astral structure in a colloid solution.[1]

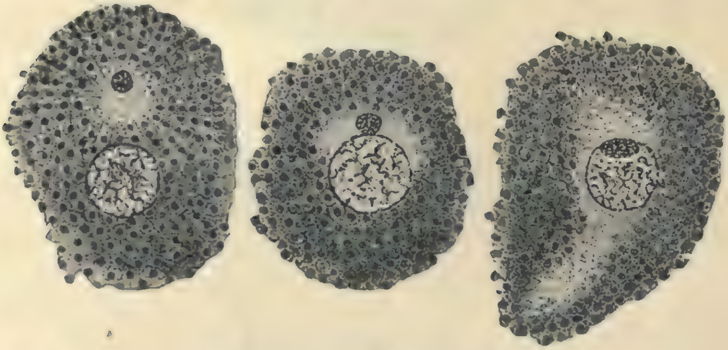

Fig. 57.—Three stages in the conjugation of male and female nucleus in the fertilisation process of *Echinus*. (From Bryce.)

Boveri and others have proved experimentally that portions of unfertilised Echinoderm ova, without egg nuclei, may develop normally after the addition of spermatozoa, while Driesch has shown that if such ova are deprived of their envelopes by shaking, and are then divided into fragments some of which contain no nuclei, the latter are capable of being fertilised a second time. It is clear, therefore, that in such cases the union of nuclei is not essential for the development of the ovum.[2]

In those ova which are surrounded by a membrane it is probable that the fertilising spermatozoön bores its way through at any point (Mammals and Amphibians). In other cases there is a small aperture in the wall of the ovum; this is called the micropyle (some Pisces and Insecta). Some eggs, however, are naked, so that the sperms may effect an entrance anywhere on the surface (some Echinoderms and Cœlenterates), or there may be funnel-shaped depressions on the egg's periphery (certain Hydromedusæ).[1]

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[1] Jenkinson, *loc. cit.* Further references are given in this paper.

[2] For references to the original papers, which are somewhat numerous, see Przibram, *Embryogeny*, English Translation, Cambridge, 1908.

In the majority of animals only one spermatozoön normally enters the ovum, but in some (certain insects, Elasmobranch fishes, reptiles, earthworm, lamprey, axolotl,[2] etc.), several may effect an entrance. The latter condition is called Polyspermy. Only one sperm-nucleus conjugates with the ovum-nucleus; the others as a general rule undergo degeneration, but in a few cases (Elasmobranchs and reptiles) they are said to divide, forming accessory nuclei whose ultimate fate is unknown.

In the hen's egg polyspermy would seem to be the normal condition, as five to twenty-five sperm have been observed in a single ovum by Patterson.[3] While only one spermatozoön unites with the egg nucleus the supernumerary ones distribute themselves throughout the margin of the blastodisc in the later phases of fertilisation and the first stages of segmentation. They undergo a certain amount of division, forming small groups of daughter nuclei, and these divisions are frequently accompanied by slight cleavage of the surrounding cytoplasm of the margin of the blastodisc, forming the accessory cleavage planes. At a later period, when the egg has reached the 32-cell stage, they have usually undergone degeneration and have disappeared.

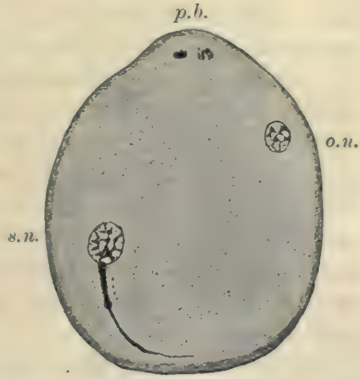

Fig. 58.—Fertilisation process in bat's ovum. (After van der Stricht.)

p.b., Polar bodies; *o.n.*, nucleus of ovum; *s.n.*, nucleus of spermatozoön.

In those animals in which only one sperm normally enters the egg, pathological polyspermy may occasionally occur. In such cases each sperm centrosome may give rise to a sperm-aster. The eggs which are fertilised in this way either do not divide at all or go on dividing irregularly for a short time and then perish.[4]

A point of considerable interest is that, in some animals, the entry of the sperm into the egg-cell takes place very early, the sperm remaining passive in the cytoplasm of the egg throughout the growth period of the ovum in the ovary. In *Histribodella*,[1] *Dinophilus*,[2] *Saccocirrus*, and a number of Turbellarians, the sperms become attached and enter the egg-cells as soon as these are differentiated in the ovary tissue, but actually fuse with the egg pronuclei only when the egg has completed its full growth and has undergone its maturation divisions. This condition has been especially studied in *Saccocirrus* by Buchner.[3]

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[1] Wilson (E. B.), *The Cell, etc.*, 2nd Edition, New York, 1900.

[2] Jenkinson, *loc. cit.* Further references are given in this paper.

[3] Patterson (J. T.), "Studies on the Early Development of the Hen's Egg," *Jour. Morph.*, vol. xxi., 1910.

[4] Wilson, *loc. cit.*

It is supposed that the entrance of supernumerary sperms is prevented normally either by some mechanical means, such as the development of a membrane formed after the penetration of the first sperm, or else by a change in the chemical constitution of the ovum occurring as the immediate result of fertilisation.[4] Thus, the brothers Hertwig[5] showed that in the case of eggs the vitality of which had been reduced artificially (*e.g.* by poisons), the vitelline membrane was formed so slowly after the entrance of the first spermatozoön that others also were able to make their way into the egg cytoplasm. On the other hand, the ova of many animals in which no membrane is formed seem to possess the capacity of resisting the entry of supernumerary spermatozoa, and the same is apparently the case with those ova which have a membrane before fertilisation, this membrane being penetrated by only a single sperm. Loeb[6] has recently suggested that polyspermy may be prevented by an alteration in the surface tension of the egg after the entrance of the spermatozoön.

McClendon[7] and Gray[8] have shown that there is a rapid drop in the electrical resistance of the ovum on fertilisation. Gray finds that in artificial fertilisation brought about by treatment of the eggs with butyric acid, this drop in resistance also takes place. A great drop in the electrical resistance of the egg is brought about by weak trivalent negative salt solutions, such as sodium citrate, while trivalent salts of the positive series such as cerium chloride, lanthanum nitrate, cause an enormous rise in resistance, when used in solutions of 0·0005 Molar strength. Harvey[1] has adduced a considerable body of evidence for believing that the egg becomes more permeable to alkalis during fertilisation. R. S. Lillie[2] has also shown that *Arbacia* eggs take several times more water after fertilisation than before.

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[1] Shearer, "The Anatomy of *Histribodella homari*," *Quar. Jour. Micr. Science*, vol. lv., 1910.

[2] Shearer, "The Problem of Sex Determination in *Dinophilus gyrocilatus*," *Quar. Jour. Micr. Science*, vol. lvii., 1912.

[3] Buchner, "Die Besamung der jugendlichen Ovocyte und die Befruchtung bei *Saccocirrus*," *Arch. f. Zellforsch.*, vol. xii., 1914.

[4] Farmer, "On the Structural Constituents of the Nucleus, etc.," Croonian Lecture, *Proc. Roy. Soc.*, B., vol. lxxix., 1907.

[5] Hertwig (O. and R.), "Beiträge zur Kenntniss der Bildung, Befruchtung und Teilung des tierischen Eies," *Morph. Jahr.*, vols. ii. and iii., 1887.

[6] Loeb (J.), *The Dynamics of Living Matter*, New York, 1906.

[7] McClendon, "Electrolytic Experiments showing Increase of Permeability of the Egg to Ions at the Beginning of Development," *Science*, N.S., vol. xxxii., 1910.

[8] Gray (J.), "The Electrical Conductivity of Echinoderm Eggs and its Bearing on the Problems of Fertilisation and Artificial Parthogenesis," *Phil. Trans. Roy. Soc. London*, Ser. B., vol. ccvii., 1916.

Brachet[3] has given a very full analysis of the conditions governing polyspermy in Amphibians. The controlling factor would seem to be the aster and centrosome. Once the egg-aster has formed, no extra spermatozoa can enter the egg under normal conditions, and even in those eggs in which polyspermy has been induced by treatment of the egg by chemical agents, or the use of very concentrated sperm emulsions, it is found that one sperm never penetrates the region of the astral rays of another sperm head. Artificial aster formation, however, can be brought about in the ripe Echinoderm egg by placing the egg in hypertonic sea-water. Harlent[4] has advanced strong evidence in a recent paper to prove that this is the rôle of hypertonic solutions in the various methods of producing artificial parthenogenesis in these animals, such as those of Loeb. Loeb found that preliminary treatment of the egg in weak solutions of a fatty acid, such as butyric, was insufficient alone to induce development; subsequent treatment in hypertonic sea-water for a few minutes was also necessary. Loeb considers that the oxidation processes set up in the ovum by the initial treatment with butyric acid go too far unless controlled by the second treatment. This, he believed, was accomplished by the hypertonic sea-water. Warburg[5] and Meyerhof,[6] however, have shown that a greatly increased consumption of oxygen takes place when the eggs are placed in hypertonic sea-water. It is probable, therefore, that hypertonic sea-water helps to initiate parthenogenetic development on account of the aster formation it produces in the cytoplasm of the ovum, which renders subsequent segmentation possible. Additional evidence on this point has been brought forward by Vlès and Dragoin,[7] who have shown that when the dividing egg is subjected to increased pressure normal aster formation does not take place, and the chromosomes are unable to take up their proper position in the cell for division.

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[1] Harvey (N.), "The Permeability and Cytolysis of Eggs," *Science*, N.S., vol. xxxii., 1910.

[2] Lillie (R. S.), "Increase of Permeability to Water following Normal and Artificial Activation of the Sea-Urchin Eggs," *Amer. Jour. of Physiol.*, vol. xl., 1916.

[3] Brachet (A.), *L'œuf et les Facteurs de l'Ontogénèse*, Paris, 1917.

[4] Hårlent, "Comment agit la solution hypertonique dans la parthénogénèse expérimentalle," *Arch. d. Zool. Exp.*, vol. lvii., 1918.

[5] Warburg, "Über die Oxydationen in lebenden Zellen," *Arch. f. ges. Physiol.*, vol. lxvi., 1910.

[6] Meyerhof, "Untersuchungen über die Warmetönung der vitalen Oxydationsvorgänge in Eiern," *Biochem. Zeitsch.*, vol. xxxv., 1911.

[7] Vlès and Dragoin, "Etudes sur la pression osmotique d'arrêt de la division cellulaire," *Arch. d. Biol.*, vol. xxxi., 1921.

In the frog it has long been known that the future axis of the embryo is determined by the point of entry and path of penetration of the spermatozoön, the head of the future embryo appearing approximately opposite the point at which the sperm has entered the ovum. Thus the future bilateral symmetry of the larva is established in the ovum before the germ nuclei have united by the path along which the sperm head penetrates the cytoplasm of the egg, in order to reach the female pronucleus.

Another change brought about in some eggs by fertilisation has been shown by certain experiments of F. Lillie.[1] He has demonstrated that the unfertilised eggs of the Polychæt *Nereis* and those of the sea-urchin *Arbacia* contain some substance that rapidly agglutinates the sperm of their own species. If watery extracts are made from the unfertilised eggs of these animals, the addition of a little of these extracts to their sperm suspended in sea-water results in their agglutination within a very short time, but similar extracts of fertilised eggs are without any action when added to sperm suspensions. He also found that extract of eggs treated with various chemical agents such as would induce artificial parthenogenesis, was also without any action in this respect. Bataillon[2] has drawn attention to the fact that the eggs of the frog after fertilisation are resistant in a high degree to the cytolysing action of hepato-pancreatic fluid. If a number of eggs of *Rana fusca* are inseminated, and are then treated in this manner, it is found that about two-thirds of their number subsequently segment in an abnormal manner, but one-third fail to divide and swell up and are cytolysed. It is found on investigation that these eggs are the ones that have failed to become fertilised.

In the Mammalia fertilisation takes place usually in the upper part of the Fallopian tube.

THE OXIDATION PROCESSES OF THE OVUM ON FERTILISATION AND DURING EARLY DEVELOPMENT[3]

Loeb was the first to advance the view that the process of the fertilisation of the ovum was one mainly concerned with oxidations taking place in the egg, initiated by the entrance of the sperm. Warburg[4] was able to show that this was definitely the case. The amount of oxygen taken up by the egg of the sea-urchin *Arbacia* on fertilisation was quantitatively measured. The oxygen disappearing from the sea-water in which the eggs had stood for some time was determined by the Winkler method, by titration with sodium thiosulphate. Warburg found that for a quantity of eggs that contained 28 milligrams of nitrogen, which roughly corresponds to about 4 million eggs, 4-5 cubic centimetres of oxygen were taken up in the course of the first hour following fertilisation. The same quantity of unfertilised eggs consumed 0·5-0·7 c.c. oxygen in this time, that is, the fertilised eggs used up six to seven times more oxygen than the unfertilised. As early cleavage and development progressed, more and more oxygen was consumed, but in the absence of oxygen all development was stopped. In the 32-cell stage 6·8 c.c. oxygen were taken up, as compared with the 4 c.c. consumed in the first hour after fertilisation. If the eggs were placed in hypertonic sea-water the normal rate of oxidation could be increased as much as ten times. In normal sea-water the fertilised eggs require a constant amount of oxygen to reach a definite stage, but this stage could be reached with half this oxygen consumption if the eggs had been entered by more than one sperm. Since there is this great increase in the respiratory exchange of the egg on fertilisation, and as this always shows a certain amount of progressive increase as development advances, it is natural to conclude that the energy liberated in the ovum by this increased oxygen consumption is correlated with the mitotic activity, and the various processes of morphogenesis taking place in the fertilised egg. It is clear, however, that this is not the case. Warburg[1] has shown that if the fertilised egg is placed in strong hypertonic sea-water, or if a little phenylurethane ($\frac{1}{2000}$ N) is added to the sea-water, all cell formation is inhibited, although the egg continues to live and undergoes a certain amount of development in the absence of cell formation. These eggs, however, consume as much oxygen as those in which normal cell formation and mitosis take place.

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[1] Lillie (F.), *Problems of Fertilisation*, Chicago University Press, 1919.

[2] Bataillon, "Nouvelle contribution à l'analyse expérimentale de la fécondation par la parthenogénèse," *Anns. Inst. Pasteur*, vol. xxx., 1916.

[3] By C. Shearer.

[4] Warburg, "Beobachtungen über die Oxydationsprozesse im Seeigelei," *Zeitsch. f. Physiol. Chem.*, vol. lvii., 1908.

Moreover the oxygen consumption of the egg obviously fails to keep pace with the increase in its morphological structure, for in the sixth hour following fertilisation, although the egg is now composed of 32 cells, the oxygen consumption has only increased from 4-6·8 c.c. per hour. In another experiment of Warburg's a larger number of eggs was used, 13·2 mg. of oxygen was consumed in the 8-cell stage, while in the 32-cell stage only 20·5 mg. was absorbed. Thus while the oxygen consumption doubled in amount, the cell structure had increased four times. In these results we also have evidence against the view that the nucleus plays the predominant part in the oxidation processes of the cell.

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[1] Warburg, "Über die Oxydationen in lebenden Zellen," *Arch. f. ges. Physiol.*, vol. lxvi., 1910.

It would appear from Masing's[1] work that there is no actual synthesis of nucleic acid in the egg-cell during early development. He found as much nucleic acid in the fertilised unsegmented egg as in the 8-cell stage. In the 8-cell stage we have eight nuclei almost the size of the nucleus of the fertilised unsegmented egg. To account for these facts Masing suggests that in the unsegmented egg, only a part of the nucleic acid is contained within the nucleus, most of it being distributed throughout the cytoplasm, but as segmentation progresses this cytoplasmic portion is gradually withdrawn within the new nuclei.

In addition to Warburg's work, Meyerhof[2] has also carried out a series of extensive researches on the energy changes taking place within the egg of the sea-urchin *Stronglocentrotus* during fertilisation and early development. The heat production of the egg was measured and correlated with the amount of oxygen consumed. The heat liberated by the eggs was determined by means of a finely divided Beckmann thermometer, the eggs being contained within a small vacuum flask, sunk in the water of a carefully regulated thermostat tank. The oxygen consumption was estimated by the Winkler method.

Meyerhof found the heat production of a quantity of unfertilised eggs, containing 140 mg. of nitrogen (about 17 million eggs), to be about 0·9 gram-calorie per hour, while the same quantity of fertilised eggs liberated 4-4·2 gram-calories in this time. In the second hour, the 2-cell stage, the heat production rose to 4·5-5 gram-calories. In the fourth hour, corresponding to the 8-cell stage, it was 6-6·5 gram-calories. In the sixth hour, the 32-cell stage, it was 9·8 gram-calories, and from this stage onwards the heat liberation increased rapidly, until in the eighteenth hour, when the free swimming stage was reached, it was 17·8 gram-calories per hour, or four times the amount in the first hour following fertilisation.

The heat given off by a known quantity of eggs, expressed in gram-calories per hour, divided by the quantity of oxygen consumed in the same time, expressed in milligrams, gave Meyerhof a calorific quotient. He found this quotient for the early stages of development to average 2·75, but if the heat of solution of carbon dioxide and its combination to form sodium bicarbonate in sea-water is taken into consideration, this value is reduced to 2·6. This figure is remarkably low, for Zünst and Schumburg, Rauber, Pflüger and others, have shown that when fat is burnt this figure should be in the vicinity of 3·3, when protein 3·2, and for carbohydrate 2·9. Meyerhof could find no carbohydrate in the egg, and there was no destruction of protein, but sufficient fat was found in the eggs to give the quotient observed.

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[1] Masing, "Über das Verhalten der Nucleinsäure bei der Furchung des Seeigeleis," *Zeitsch. f. Physiol. Chem.*, vol. lxvii., 1910.

[2] Meyerhof, "Untersuchungen über die Warmetönung der vitalen Oxydationsvorgänge in Eiern," I., II., III., *Biochem. Zeit.*, vol. xxxv., 1911.

The most important fact arising from Meyerhof's experiments was that whether he took the unfertilised egg, the fertilised, or the fertilised egg treated with phenylurethane, in which cell division had been inhibited, the value of his calorific quotient was always the same. If any of the chemical energy liberated in the egg, as the result of the oxygen consumption, was utilised in any of the processes of morphogenesis, these values could not be the same in every instance. In the case of fresh sperm, the calorific quotient was 3·1, or something approaching normal. The evidence both of the oxygen consumption and the heat liberation of the developing egg, then, seems to show there is little direct connection between the oxidations taking place, and the appearance of visible morphological structure, and this is borne out by the calorific quotient, which is the same for the fertilised segmenting and the unfertilised egg.

If the energy of the egg is not employed in this manner how is it utilised? Warburg[1] suggests that it is used in performing work which is indispensable to the life of the cell. Thus it might be used in keeping certain constituents of the cytoplasm apart, holding the cell-membrane intact and semipermeable, in which respect the electric charge on the surface plays so important a part as the experiments of Girard[2] show. That the cytoplasm of egg-cell in the living state is sharply divided into a number of regions, in which different reactions are taking place, has been clearly demonstrated by the microdissection methods of Chambers,[3] Kite,[4] Barber,[5] and Seifriz.[6] These, then, are a few of the ways in which this energy of the cell might be utilised.

It has been long recognised by morphologists that cellular structure is no criterion of organisation, for many of the Protozoa possess an organisation more complex than many of the simpler Metazoa. Moreover, many animal eggs, such as those of the Cephalopod *Loligo*, and many Arthropod eggs, begin to assume the shape of the future larval form through which they will subsequently pass in their ontogenetic history before any cleavage has taken place, clearly showing preformation in this respect.

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[1] Warburg, "Beiträge zur Physiologie der Zellen," *Ergebnisse der Physiologie*, vol. xiv., 1914.

[2] Girard, "Scheme physique pour servir à l'étude de la nutrition minerale de la cellule," *Compt. Rend. Acad. de Science Paris*, vol. clxviii., 1919.

[3] Chambers (R.), "Microdissection Studies," I. and II., *Amer. Jour. of Physiol.*, vol. xliii., 1917, and *Jour. of Exp. Zool.*, vol. xxiii., 1917.

[4] Kite, "Studies on the Physical Properties of Protoplasm," *Amer. Jour. of Physiol.*, vol. xxxii., 1913.

[5] Barber, "The Pipette Method in the Isolation of Single Micro-organisms and in the Inoculation of Substances into the Living Cells," *Phillip. Jour. Science*, vol. ix., 1914.

[6] Seifriz, "Viscosity Values of Protoplasm as Determined by Microdissection," *Bot. Gaz.*, vol. lxx., 1920.

In many eggs, again, the entrance of the sperm is followed by rapid changes in the viscosity of the cytoplasm, followed by streaming effects within the egg. In the Ascidian *Cynthia*, Conklin[1] has shown that the cytoplasm of the ripe egg consists of a grey yolky substance occupying the centre of the egg, and surrounded by a peripheral layer of bright yellow pigmented cytoplasm, while at the animal pole is an area of clear cytoplasm, the germinal vesicle. On the entrance of the spermatozoön, an immediate rearrangement of these materials takes place. The yellow cytoplasm now streams down to the negative pole of the egg and arranges itself symmetrically with regard to the egg axis, while the clear cytoplasm of the germinal vesicle comes to lie above it. The grey yolk now lies at the animal pole containing the female pronucleus embedded in it.

That the entrance of the sperm into the egg of the sea-urchin initiates some structural mechanism in the egg, by virtue of which its high rate of oxidation in the fertilised condition is rendered possible, would seem to be borne out by experiments of Warburg and Meyerhof.[2] They found that, if they ground up the eggs with sand and sea-water to a fine paste, the unfertilised eggs consumed just as much oxygen in the broken condition as when intact and whole. There was only a slight and very insignificant fall in the respiratory quotient. If the fertilised eggs were reduced to a paste, then, instead of this having the normal respiratory quotient characteristic of the fertilised egg, it was invariably a third or fourth of this amount. Thus the rubbing up with sand made little difference in the case of the unfertilised egg, but was followed in the fertilised egg by an enormous drop in the respiratory quotient. That this mechanism is not bound up in any way with the usual visible structure of the egg is shown by further experiments, in which the eggs were treated with acetone. It was found that acetone is an excellent fixative for the egg, preserving the minute details of microscopical structure and chemical composition unchanged; even the egg lipoids seemed unaffected by the use of acetone. In the case of the unfertilised egg, not a great deal of difference between the eggs treated with acetone and the untreated could be observed; both consumed almost the same quantity of oxygen. In the case of the fertilised eggs there was again, as with the eggs rubbed with sand, an enormous drop in the respiration. The eggs after treatment with acetone can even be dried, when they can be reduced to a very fine powder. This powder, when dissolved in water, still shows considerable respiratory power. The unfertilised acetone egg powder, however, shows almost as much consumption of oxygen as the intact egg, while the fertilised acetone egg powder shows a drop of over 90 per cent. in its power of consuming oxygen. None of these egg powders give off CO_2.

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[1] Conklin, "The Organisation and Cell Lineage of the Ascidian Egg," *Jour. Acad. Nat. Science Phila.*, vol. xiii., 1905.

[2] Warburg and Meyerhof, "Über Atmung in abgetöteten Zellen und Zellenfragmenten," *Arch. f. ges. Physiol.*, vol. cxlviii., 1912.

In the more recent work on the oxygen consumption of the egg, the Winkler titration method has been superseded by the more accurate and convenient Barcroft differential manometer method. The advantage gained by the use of the manometer is that continuous observations can be made on the same material, and the respiratory exchange can thus be followed minute by minute.

Warburg[1] (1915), using this instrument, has made a reinvestigation of the respiratory exchange of the egg of *Stronglocentrotus* during the first twenty-four hours of development. He found that a quantity of unfertilised eggs that contained 20 mg. of nitrogen, at a temperature of 23° C. consumed 10-14 cubic millimetres of oxygen in twenty minutes. The fertilised egg, ten minutes after the addition of the sperm, consumed 60-84 cub. mm. under the same conditions. That is, ten minutes after fertilisation the oxygen consumption of the egg was 6 times greater than before fertilisation. In the sixth hour the oxygen consumption was 12 times that of the unfertilised egg, at twelve hours 16 times; while at twenty-four hours it was 22 times the amount of the unfertilised egg. As Warburg states, it is highly remarkable that in one and the same cell substance, which receives no addition of fresh material from any external source, we should find, as the result of fertilisation, in the course of twenty-four hours a rise in its oxidation rate equivalent to something like 2,000 per cent.

On the whole the manometer seemed to show that there was a much closer agreement between the increase in the respiratory quotient and the growth of visible structure of the egg. In all instances the CO_2 output of the eggs follows the oxygen consumption very closely, the respiratory quotient being about 0·9. The respiration of a single spermatozoön was found to be 1,500-2,000 times smaller than the egg.

In the past season the investigation of the problem has been carried a step farther[1] by the employment of a special type of the manometer, in which it was possible to bring about the fertilisation of the eggs within the closed chambers of the apparatus. It was then possible to observe the respiration of the egg at the actual moment of entry of the sperm. The eggs and sperm of *Echinus microtuberculatus* were used. On the addition of the sperm to the eggs there is always an immediate and almost instantaneous consumption of oxygen by the eggs. In the course of the first minute the uptake of oxygen is many times that of the same eggs one minute before the addition of the sperm, and more is usually taken up in the first minute than is taken up in the second, third, and fourth minutes, after the addition of the sperm, taken altogether.

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[1] Warburg, "Notizen zu Entwicklungsphysiologie des Seeigeleies," *Arch. f. ges. Physiol.*, vol. clx., 1915.

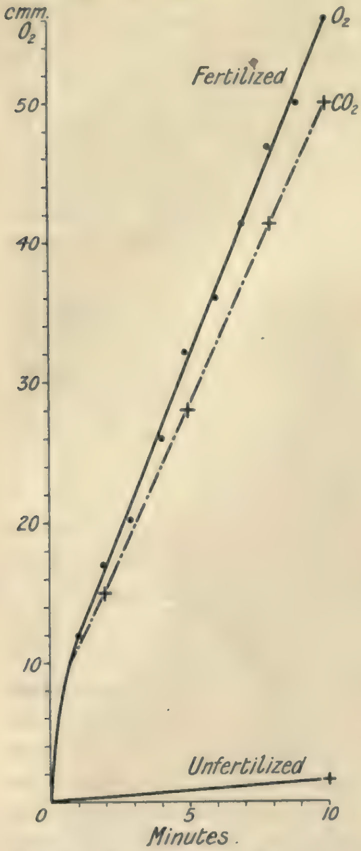

Fig. 59.—Chart showing the amount of oxygen taken up, and the carbon dioxide given off, in the first ten minutes after the addition of the sperm to the eggs of *Echinus microtuberculatus*, 56 cub. mm. of oxygen being taken up by the fertilised egg in this time, as compared with 1·5 cub. mm. oxygen consumed by the same eggs in the unfertilised condition in the same interval.

Unbroken curve = oxygen; broken curve = carbon dioxide.

Respiratory quotient, about 0·9. Half a million eggs (4·06 mg. egg nitrogen). Temp., 14·5° C. Bar. 760 mm. Hg.

In all instances the CO_2 output of the eggs follows the oxygen uptake very closely, the respiratory quotient being in the neighbourhood of 0·92.

At standard barometric pressure, and temperature of 14·5° C., it was found that 4·06 mg. of egg nitrogen (½ million eggs) before fertilisation consumed 1·5 cub. mm. of oxygen in ten minutes; after fertilisation the same eggs consumed 56 cub. mm. in this time; there was thus an increase in the respiratory quotient of the eggs ten minutes after fertilisation of something like thirty-seven times that of the unfertilised condition. If we consider the increase taking place at the end of the first minute after the addition of the sperm to the eggs, we get even more striking figures. The oxygen consumption of the unfertilised egg is so low, however, that its measurement for so short a time is difficult with the quantity of eggs usually employed ($\frac{1}{2}$ to 1 million eggs) in an experiment, as usually no reading can

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[1] Shearer, "On the Oxidation Processes of the Echinoderm Egg during Fertilisation," *Proc. Roy. Soc. London*, B., vol. xciii., 1922.

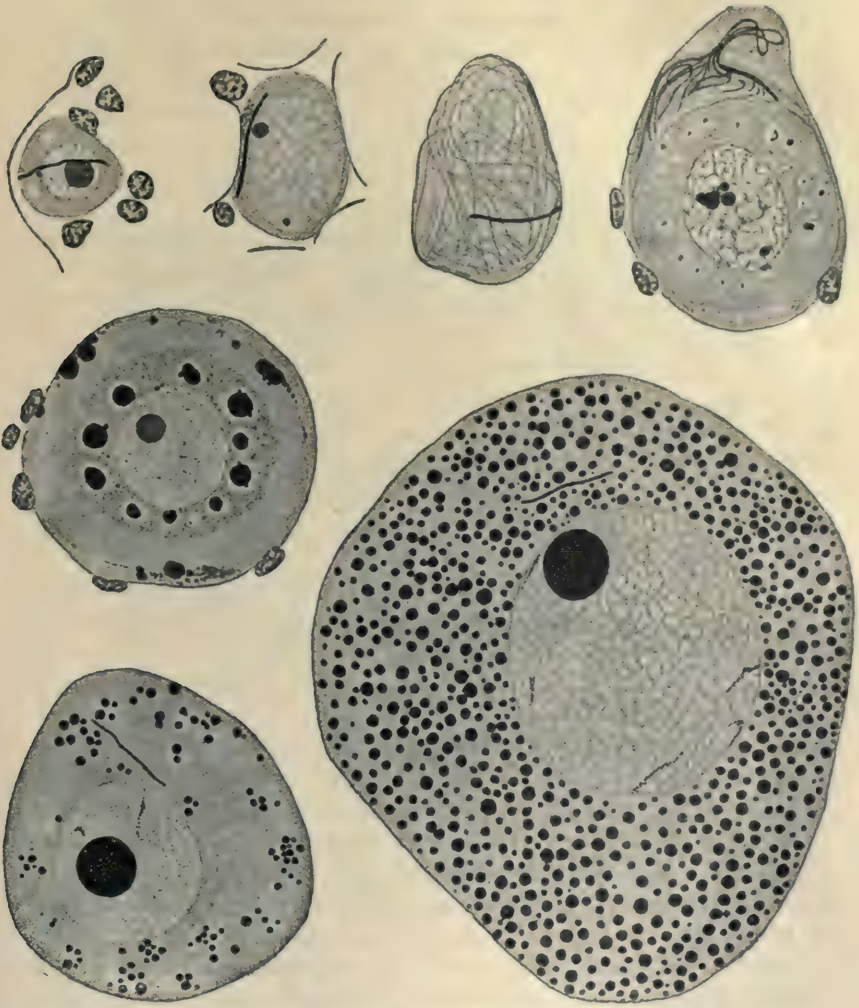

Fig. 60.—The insemination of the eggs of *Saccocirrus* while these are undergoing growth in the ovarian tissue. The long black rod-like body in the cytoplasm of the primitive ovocytes is the spermatozoön. It will be seen that the ovum develops from a very early stage with the spermatozoön in its cytoplasm, actual fusion of sperm and female pronucleus only taking place after the eggs are laid and have undergone meiosis. (From Buchner's *Praktikum der Zellenlehre*, Bd. i., Borntraeger.)

be observed on the manometer scale. If we take the reading on the unfertilised eggs at the end of ten minutes, we can probably approximate to it roughly by dividing this figure by 10. It works out for a number of experiments at something like 0·15 cub. mm. of oxygen per minute. The same eggs fertilised consume in the first minute after the addition of the sperm 12 cub. mm. of oxygen. Thus the addition of the sperm to the eggs causes, within the space of one minute, an increase in their oxygen consumption of something like eighty times that observed on the same lot of eggs one minute previous to the addition of the sperm.

The examination of sections of fixed material of these fertilised eggs shows that the process is by no means an instantaneous one, and that the sperm take ten to fifteen minutes before they find their way into the actual cytoplasm of the eggs.

This initial oxygen consumption of the egg immediately on fertilisation must be induced by the first contact of the sperm with the external surface of the egg-membrane. We arrive then at the remarkable conclusion that mere contact of the spermatozoön with the external surface of the egg-membrane is capable of increasing the oxygen consumption of the egg by something like 8,000 per cent. in the course of one minute.

There are good reasons for believing, as the result of Loeb's experiments on the fertilisation of the eggs of *Stronglocentrotus* with the sperm of *Asterias*, and Lillie's description of the process of fertilisation in *Nereis*, that the entry of the spermatozoön into the egg consists of two distinct phases. First, an external one, in which certain changes are brought about in the cortical substance of the egg the moment the sperm make contact with the external surface of the egg-membrane. This would seem to be correlated with this initial oxidation taking place in the egg as described above for *E. microtuberculatus*. Secondly, the changes following the actual entry of the spermatozoön into the egg cytoplasm itself, which, as Lillie has shown in *Nereis*, only takes place some thirty minutes after the first phase of fertilisation, and in the sea-urchin, follows some ten to fifteen minutes after the sperm are added to the eggs.

By centrifuging the eggs of *Nereis* before the sperm has actually penetrated the egg-membrane, Lillie was able to separate the jelly surrounding the egg and containing the spermatozoön from the egg itself. These eggs complete meiosis which has been initiated by the spermatozoön, but never segment. A typical segmentation nucleus is, however, formed, which breaks down, leaving the chromosomes free in the egg cytoplasm; they split longitudinally in the normal manner but never separate. No asters or mitotic spindles appear in these eggs, as when the complete process of fertilisation is allowed to take place, and in the absence of these structures the process of cell division makes no further progress, and the chromosomes finally degenerate and break down. This experiment clearly proves that the sperm bring about profound alterations in the egg while still external to the egg-membrane. Loeb has shown that when the eggs of *Stronglocentrotus* are fertilised with the sperm of *Asterias*, in hyper-alkaline sea-water, they only form fertilisation membranes; no actual segmentation takes place unless the eggs receive further treatment so that artificial parthenogenesis is induced (see p. 236).

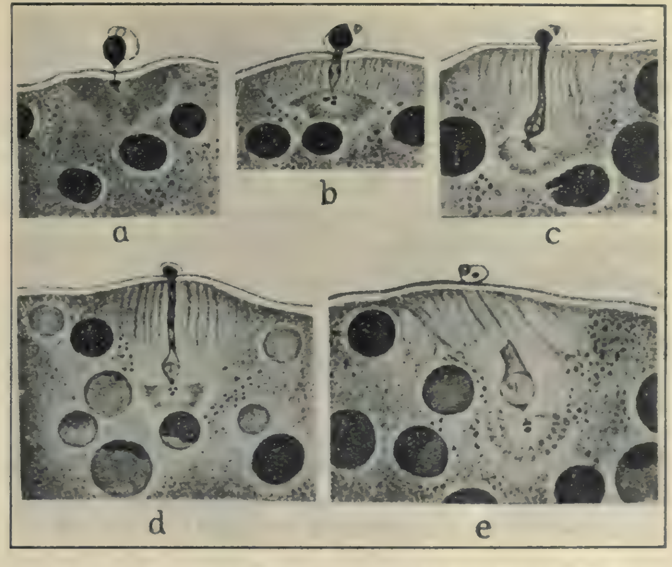

Fig. 61.—The entrance of the spermatozoön into the egg of *Nereis*.

Penetration of the spermatozoön in the egg of *Nereis*, from sections: *a*, thirty-seven minutes after insemination; *b*, *c*, *d*, three stages from eggs killed forty-eight and a half minutes after insemination; *e*, fifty-four minutes after insemination; the head of the spermatozoön now entirely within the egg is contracting while the middle-piece of the spermatozoön remains on the egg-membrane; it never enters the egg; the tail also remains outside. (From Lillie's *Problems of Fertilisation*, University of Chicago Press.)

Meyerhof and Warburg in many of their experiments have shown that any injury or cytolysis of the egg-membrane is invariably followed by a great increase in the oxygen consumption of these eggs. Meyerhof[1] found that this is usually accompanied by an increased liberation of heat. In eggs treated with weak solutions of NaCl in which the normal condition of the cell wall is destroyed in the absence of Ca and K ions, the rise of oxygen consumption was five times that of the same quantity of untreated eggs. The heat production was increased from 0·9 gram-calorie per hour to 3·4 gram-calories per hour, after treatment with valerianic acid by which artificial membrane formation was induced.

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[1] Meyerhof, "Die Atmung der Seeigeleier (*S. lividus*) in reinen Chlornatriumlösungen," *Biochem. Zeit.*, vol. xxxiii., 1911.

A great many of Loeb's and Warburg's experiments point conclusively to the cortical layer of the egg and the egg-membrane as being the controlling factors in the oxidation processes of the egg. Any change brought about in these is immediately reflected in the oxygen uptake of the egg. Loeb has, of course, based his method of producing artificial parthenogenesis on the fact that alteration of the surface layer of the egg renders the commencement of development possible. But how can the cytolytic destruction of the surface layer of the egg lead to development? Warburg has shown that there are good reasons for believing that the oxidations taking place in the egg occur mainly at its surface, for NaOH, which does not diffuse into the egg, raises the rate of oxidations more than NH_4OH, which readily diffuses into the egg.

Moreover, he found[1] that the addition of iron salts to the broken-up eggs, or acetone egg powder, was followed by a considerable increase in the oxygen consumption of these egg preparations, and he found marked traces of iron in the sea-urchin egg. He suggests that the iron probably acts the part of a catalyser. If the iron were located in the lipoid layer of the egg in a condition in which it was unable to act, some slight alteration in this layer, due to the action of the sperm, might render it active or bring both the iron and the oxidisable substrate into a condition in which they could quickly interact. We know from Thunberg's work[2] that lecithin in a watery suspension consumes considerable oxygen in the presence of iron salts. The egg of the sea-urchin contains considerable quantities of this lipoid.

Warburg has pointed out that there are many respects in which the metabolism of the fertilised egg resembles that of the yeast-cell. In each it has been shown that structure plays a very important part, as both acetone preparations of the egg and the yeast-cell retain considerable respiratory power. Meyerhof[3] finds, however, that if acetone yeast is well washed with water, it soon loses its capacity to take up oxygen. If a little watery extract of yeast is added to the washed yeast it immediately regains its lost respiratory power. In the water used in washing the yeast Meyerhof found the presence of some compound containing the (SH) group. Hopkins has recently isolated from the yeast-cell a substance which is undoubtedly closely related, if not identical with this respiratory body of Meyerhof. It proves to be a combination of two amino-acids, glutamic acid and cystine, to which Hopkins[1] has given the name of *Glutathione.* This dipeptide possesses most remarkable properties in that, in the reduced (SH) form, it can take up molecular oxygen, while in the oxidised (S-S) form so produced it can act as a hydrogen acceptor, and can catalyse oxidations of the Wieland type, in which no activation of oxygen probably takes place, but an activation of hydrogen occurs instead. In the presence of a suitable acceptor the hydrogen is removed and the oxidation of the original substance takes place. It can therefore be both reduced and oxidised under the influence of factors known to be present in the tissues themselves. Moreover, it possesses precisely those properties which a co-ferment adapted to an oxidase system would possess, and at present stands entirely in a class by itself. Hopkins has shown that it is present in most living cells, but he could find no trace of it in the hen's egg, although it was very obviously present in the thirty-hour chick embryo. I find, however, that in the ripe eggs and sperm of the sea-urchin *Echinus miliaris*, it is invariably present in very appreciable quantity, but one minute after fertilisation the same eggs give a very pronounced magenta colour by the nitro-prusside test. It is very readily washed out of the eggs by heating them in sea-water in the presence of a little acetic acid ; when its presence can be shown in the water, the washed eggs then no longer give the test. In the unripe egg, in which the egg nucleus is plainly visible, in a number of instances I could find no trace of its presence. In the ripe eggs it is present in very variable quantities, the eggs of no two females giving the same result, probably depending on varying degrees of ripeness of their gonads. In several samples of ripe sperm it was present in much greater quantity than in any of the eggs examined. There are many points of interest brought up by the presence of this remarkable substance in the fertilised egg, and there is every reason to believe its study in the future will reveal many interesting facts with regard to the respiratory exchange in the egg on fertilisation.[2]

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[1] Warburg, "Über die Rolle des Eisens in der Atmung des Seeigeleis nebst Bemerkungen über einige durch Eisen beschleunigten Oxydationen," *Zeitsch. Physiol. Chem.*, vol. xcii., 1914.

[2] Thunberg, "Untersuchungen über autoxydable Substanzen und autoxydable Systeme von physiologischen Interesse," *Skand. Arch. Physiol.*, vol. xxiv., 1911.

[3] Meyerhof, "Untersuchungen zur Atmung getöteter Zellen," *Archiv. f. ges. Physiol.*, vol. clxx., 1918.

The Hereditary Effects of Fertilisation

The attempts that have been made to interpret the nature and essence of sexual reproduction may be ranged under two heads, representing the two chief theories that have been elaborated (with some modifications by their respective adherents) to explain the observed phenomena.[1] According to one hypothesis, conjugation of the gametes results in a rejuvenescence which is essential for the perpetuation of the race (see p. 221). According to the second theory, which is not necessarily antagonistic to the first, gametic union is a source of variation.[2] The latter theory may now be briefly considered. A full discussion of the hereditary effects of fertilisation is, however, beyond the scope of the present work.

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[1] Hopkins, "On an Autoxidisable Constituent of the Cell," *Biochem. Jour.*, vol. xv., 1921.

[2] Shearer, "On the Oxidation Processes of the Echinoderm Egg during Fertilisation," *Proc. Roy. Soc. London*, B., vol. xciii., 1922.

The doctrine that conjugation is a source of variation was first promulgated at the beginning of the last century by Treviranus. Subsequently Brooks[3] adopted the same idea, and Weismann made it the basis of his famous theory of heredity.[4] "Sexual reproduction is well known to consist in the fusion of two contrasted reproductive cells, or perhaps even in the fusion of their nuclei alone. These reproductive cells contain the germinal material or germ-plasm, and this again, in its specific molecular structure, is the bearer of the hereditary tendencies of the organisms from which the reproductive cells originate. Thus, in sexual reproduction, two hereditary tendencies are in a sense intermingled. In this mingling I see the cause of the hereditary individual characteristics; and in the production of these characters the task of sexual reproduction. It has to supply the material for the individual differences from which selection produces new species."

Weismann supposes the nuclear chromatin of the cell to consist of a large number of self-propagating vital units which he calls biophors. These biophors he believes to be grouped together to form more complex units, named determinants, which represent the separate parts of the organism. The determinants are supposed to be aggregated together to comprise units of a still higher order, known as ids. These are identified with the chromatin granules. Every part of the organism (or every character that it possesses) is believed to be represented in an id. Moreover, Weismann assumes that the ids vary slightly in related individuals, the differences in the ids corresponding with the variations in the species. Lastly, the ids are said to be arrayed in linear series so as to form idants. Weismann identifies these with the chromosomes. It follows, therefore, that each chromosome represents a particular group of slightly differing germ-plasms. The purpose of variation, as expressed in the terms of this theory, is to produce new combinations of heritable variations by the mixture of different ids. And since the number of chromosomes, and consequently the number of ids, is doubled as a result of the conjugating process, the complexity of the chromatin would become indefinitely increased if there were no periodic reduction. But this, according to Weismann, is provided against in the maturation process of the gametes, when the quantity of chromatin in the cells becomes reduced by one-half, as described in the preceding chapters.

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[1] For accounts of the various theories which have been put forward concerning the nature of fertilisation, see Wilson, *loc. cit.*, Geddes and Thomson, *The Evolution of Sex*, 2nd Edition, London, 1901; Weismann, *The Evolution Theory*, English Translation, London, 1904; and Lock, *Variation, etc.*, London, 1906. Further references are given in these works.

[2] A third theory, which has never obtained any great support among biologists, suggests that the purpose of sexual reproduction may be to prevent variation, and so preserve specific uniformity. According to this view the sexual process, although continually creating new variations, is also constantly obliterating them by tending to produce individuals possessing the mean of their parents' characters. This theory, which is the converse of the second theory referred to in the text, has received the support of the Hertwigs. In this connection it may be remarked that variability is quite as great among non-sexual parthenogenetic animals as among those which are reproduced sexually. This fact is difficult to explain if we adopt the theory that the purpose of gametic union is to induce variability. Moreover, Enriques ("La Coniugazione e il differenziamento sessuale negli Infusori," *Arch. f. Protistenkunde*, vol. ix., 1907), as a result of a series of experiments upon conjugation in Infusoria, has adopted a similar view to that of the Hertwigs.

[3] Brooks, *The Law of Heredity*, Baltimore, 1883.

[4] Weismann, *The Germ-Plasm*, English Translation, London, 1893.

The reduced number of chromosomes is supposed to contain all the primary constituents of each of the two parents. And what is more, according to this theory, every gamete contains ids which are derived, not only from both the parents, but also from the ancestors, all the immediate ancestors being represented.

Weismann's theory of the nature of fertilisation was accepted by many biologists as a working hypothesis until the disinterment of Mendel's discovery about twenty years ago. The confirmation of this discovery by numerous workers in different fields has led to a revision of many of Weismann's conceptions.

The original experiments of Mendel[1] were upon hybridisation in peas, the two parent varieties initially selected differing from each other in one particular character. The hybrids produced by crossing were all similar superficially, and resembled one of the parents in the character in question, which was therefore called the dominant character, the other character being known as recessive. When the hybrids were crossed among themselves, approximately one-half of the offspring were found to be identical with their hybrid parents (dominant hybrids), one-quarter resembled one of the original varieties (the grandparent with the dominant character), while the remaining quarter were like the other pure variety (the grandparent with the recessive character). Consequently the pure dominants and the dominant hybrids resembled one another outwardly, but they differed in their capacity to transmit the characteristics in question, since the pure dominants alone were capable of always breeding true. The recessives also invariably bred true. Mendel drew the conclusion that in the hybrid the gametes (both male and female) were of two kinds, which were respectively identical with the two kinds represented by the gametes of the original pure varieties. The differentiation of gametes carrying different characters is the essential principle in Mendel's theory, the existence of dominant and recessive characters, though often observable, being by no means universal.

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[1] Mendel, "Versuche über Pflanzen Hybriden," *Verh. natur. f. Ver.*, in Brünn, vol. iv., 1865. Reprinted in English in *Mendel's Principles of Heredity* (Bateson), Cambridge, 1902. Mendel's work was rediscovered and confirmed by de Vries, Correns, and Tchermak in 1900, and subsequently by Bateson and a large number of other workers. For a general account of the Mendelian theory, and numerous references to the literature of the subject, see Bateson, *loc. cit.*; also Bateson, Saunders, Punnett, and Hurst, etc., in *Reports to the Evolution Committee of the Royal Society*, Parts I., II., III., IV., and V., 1902, 1905, 1906, and 1909; Punnett, *Mendelism*, 5th Edition, London, 1919; and Morgan, *The Physical Basis of Heredity*, Philadelphia and London, 1920.

Another example, taken from the work of Bateson and Punnett, will be sufficient to elucidate further the Mendelian conception of gametic differentiation. Breeders of blue Andalusian fowls have always recognised the practical impossibility of obtaining a pure strain of this breed. However carefully the birds are selected they invariably produce two sorts of "wasters," some being pure black, and some white with irregular black marks or splashes. Bateson and Punnett were the first to supply the explanation. They found that, on breeding from a large number of blue Andalusian fowls, on an average half of the offspring were blue like the parents, a quarter were black, and a quarter were "splashed-white." They consequently drew the conclusion that the mechanism of inheritance in the Andalusian fowl is comparable to what Mendel supposed to exist in his hybrid peas. The gametes of the breed, according to this hypothesis, instead of being all similar and carrying the blue character (as one would suppose on Weismann's theory), are of two different kinds, those of the one kind being bearers of the black character, and those of the other being bearers of the splashed-white character. Such gametes, uniting by chance when the fowls mate together, give rise to three kinds of offspring, one black-white (becoming blue, actually, like the parents), one black-black, and one white-white, these appearing (on an average) in the proportion of 2 : 1 : 1 according to the law of probability. In this particular case of Mendelian inheritance, neither of the two alternative parent characters (*i.e.* neither black nor splashed-white) is dominant and neither is recessive. Why black-bearing gametes uniting with white-bearing gametes should give rise to blue individuals the Mendelian theory does not attempt to explain.

The importance of Mendel's discovery lies in the fact that it forms the basis of a theory whereby variability can be discussed in terms of the conjugating cells themselves, and not merely in terms of the resulting zygotes. Moreover, it is a theory which has been found to be applicable to a very wide class of facts; and it differs from other theories of heredity in that it stands the test of a true scientific hypothesis in enabling one to predict phenomena which on no other theory could be predicted.[1] There are reasons for supposing that sex may be a Mendelian phenomenon; that is to say, that the ova and spermatozoa are themselves sexual entities prior to conjugation (see p. 671). It still remains to be proved, however, that the principles underlying Mendel's theory are applicable to all forms of inheritance.[2]

It has been mentioned that on Weismann's hypothesis every gamete contains ids representing both its parents and all its immediate ancestors. On the other hand, according to the Mendelian theory, although all the essential characters of the organism are represented in each germ-cell, the Mendelian characters, or allelomorphs as they are called, are each represented by paternal or maternal ids only, and not by both, while the immediate ancestors have no representation at all. It has been supposed that the chromatin granules (which Weismann identified with the ids) are the carriers of the Mendelian allelomorphs, and that when these fuse together during the conjugation of the chromosomes which precedes the process of reduction (see p. 125), there is an exchange of allelomorphs between the chromosomes.[3] If this interpretation is correct, it is simply a matter of chance whether an allelomorph remains in the chromosome which originally contained it, or becomes transferred to the other chromosome of the conjugating pair. And since each of the two chromosomes passes into a different product of cell division, the allelomorphs would become distributed in precisely the kind of way that the Mendelian theory postulates.[4]

The Mendelian investigators have shown that by experimental breeding it is apparently possible to superimpose certain characters belonging originally to one kind of individual, upon different characters belonging to another kind, thus creating new combinations of characters. Thus it is claimed that by starting with two individuals, each possessing two unit or allelomorphic characters, which we may call A and X (associated together in one individual) and B and Y (associated in the other), it is possible in two generations to produce new individuals in which the combinations are interchanged, A being associated with Y, and B with X.[1] It has been claimed also, that, in spite of the new combinations, each of the original separate unit characters can be preserved in a state of complete purity, and without in any way affecting, or being affected by, the characters upon which they have been superimposed. By resorting to such methods, it has been thought possible to build up, little by little, entirely fresh types of organisms, possessing new combinations of pure characters, which previously existed only in different individuals.

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[1] Marshall, "The Categories of Biological Science," *Mind*, vol. xxix., (Jan., 1920.

[2] *Cf.* Darbishire, "Recent Advances in Animal Breeding," *Royal Horticultural Society's Report of the Conference on Genetics*, London, 1907.

[3] For the evidence see Morgan, *loc. cit.*

[4] Lock, *loc. cit.*

It remains to be considered how far this conception of an organism as an individual capable of description in terms of unit characters (each of which can be transmitted pure) is in harmony with modern physiological theory, or justified by experimental investigation.

In the first place, it may be pointed out that the entire trend of physiological research in recent years has been to show that the correlation that exists even between remote parts of the body is often extraordinarily close, and that in all probability there is not an organ or structure that is not dependent in its growth and activity upon chemical substances, elaborated by other and sometimes distant parts of the body, and carried thence in the circulating blood. Thus a change in the whole metabolism, producing palpable modification in whole groups of characters, may be induced experimentally in the individual, by interfering with or removing one particular organ. This is well shown in the various kinds of correlation existing between the organs of internal secretion. Again, a change in the environment may directly affect the metabolism, and so influence all the characters of the body. To the physiologist, therefore, a so-called unit character cannot readily be regarded as something represented by a substance located originally in a chromosome or chromomere. Such a view, as Verworn[2] remarks, is "too morphologically conceived." It is more in keeping with the physiological view of life to regard the characters of the individual as manifestations of a particular kind of metabolism, which is itself partly the outcome of environmental influences, and partly the developmental result of the sort of metabolism that existed in the germ-cells from which the organism was derived. According to this view, it is clear that the presence of any one characteristic may exert an influence upon many, if not upon all, the other characteristics, and that, even in heredity, one cannot hope to alter any single organ or structure without affecting, in some slight degree at any rate, all, or nearly all, the other parts of the body. It may be argued, therefore, in criticism of the Mendelian conception of unit characters, that it takes little or no account of the metabolism of the organism as a whole. Thus it has been shown that in the case of presence or absence of hair pigment (which has been regarded as a simple example of alternate characters, such as can be superimposed experimentally upon other characters in the course of two generations), there is a pronounced correlation between albinism and other characteristics of the body, these characteristics depending for their existence upon a common metabolism. Moreover, the difficulty experienced by Wood[1] in superimposing the complete hornlessness of Suffolk sheep upon the white face of the Dorset horns, is probably another example of the physiological correlation subsisting between different, and apparently unconnected, structures. Originally, this case was regarded as one of simple superposition, and Bateson[2] describes the hornless character as having been transmitted "pure," but subsequently many of the so-called hornless sheep were found to have grown scurs. The explanation which I tentatively suggest is, that the character of pure hornlessness was somehow or other incompatible with the pure white-faced character, these two characters being ordinarily indications of two sorts of metabolism, in just the same kind of way as the beef-producing quality and the milk-producing quality seem to be to some extent incompatible in cattle. I am inclined to go further, and to suspect that many of the other Mendelian cases, when examined more critically, will show that no one character can be superimposed upon another, in experimental breeding, without altering, though perhaps only very slightly, the character upon which it has been superimposed.

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[1] The first filial generation is spoken of as the F_1 generation, the second filial generation as the F_2, and so on.

[2] Verworn, *loc. cit.*

Experiments in which Merino rams were crossed with Shropshire ewes[3] have shown that the more important characteristics of the body or carcass (that is to say, the "mutton points") may be transmitted to the third generation so as to reappear in new combinations in the cross-bred sheep. Thus taking the four points, "over the shoulder," "behind the shoulder," "top of leg," and "loin," which are widely different in Merinos and Shropshires (being

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[1] Wood (T. B.), "The Inheritance of Horns and Face-Colour in Sheep," *Jour. Agric. Science*, vol. iii., 1909.

[2] Bateson, *Mendel's Principles of Heredity*, Cambridge, 1909. No doubt, however, it is arguable that the scurs themselves represent unit characters, and that if the scurs are of different kinds, these also represent unit characters (which have hitherto somehow remained "latent"), and that if they occur with different degrees of development, these again are unit characters. And so on.

[3] Mackenzie and Marshall, "The Inheritance of Mutton Points in Sheep," *Trans. Highland and Agric. Soc.*, 1917.

"bad" in the former and "good" in the latter in regard to mutton production), segregation appeared very clearly in animals of both the second and third generations, the points being reproduced in all possible combinations among the cross-bred sheep. This case of Mendelian transmission is all the more remarkable in that the characters are not superficial but deep-seated and relating to bodily conformation, each of them depending on a number of anatomical factors. It cannot be said, however, that all the characters were inherited "pure" or without being influenced by the other characters with which they entered into new combinations, and in some cases the points shown were definitely composite, being dissimilar to those of both the parent breeds.

When, as a consequence of cross-breeding two varieties, the alteration of the parent characteristics is minimal the transmission of pure characters—according to Mendelian expectation—may be said to occur, and experimental evidence has shown that there are considerable numbers of such cases. It is a legitimate field of work for the biometrical school of biology to determine by statistical methods the extent to which variation occurs as a result of attempted superposition of characters which in their "pure" state are physiologically incompatible. Furthermore, a latent character may be regarded as one, the outward manifestation of which is incompatible with the existing kind of metabolism, but which is capable of reappearance as soon as the conditions become favourable. But because it is helpful to assume that latent characters are present in some manner in the animal organisation, it is not necessary to assume that they are definitely located in the nuclei of germ-cells or in any other particular structures[1] (see pp. 674-675).

Moreover, it should be remembered that there is no experimental proof that the chromosomes of the gametes constitute the entire physical basis of inheritance. The best evidence in support of this supposition appears to be Boveri's experiment, in which he fertilised a non-nucleated ovum of one species of sea-urchin with the spermatozoön of another species.[2] The resulting pluteus or larva was purely paternal in its characters. Boveri concluded, therefore, that this result was due to the introduced nucleus, the maternal cytoplasm having no determining effect upon the offspring, but merely supplying the material upon which the sperm operated.[1] Seeliger,[2] Morgan,[3] and others have objected to Boveri's conclusion on the ground that larvæ arising from cross-fertilisation show an unusually wide range of variation. Moreover, Godlewsky[4] has carried out an experiment in which he fertilised a non-nucleated portion of a sea-urchin's egg with the spermatozoön of a crinoid, and obtained, as a result, a larva of the maternal type. This experiment, if correctly described, seems to nullify Boveri's conclusion.

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[1] The attempt to locate latent characters of organisms in particular parts of the germ-cells should perhaps be regarded as a survival from a time when all kinds of qualities, abstract or otherwise, were supposed to reside in definitely restricted positions. Compare Phenology. The centres in the nervous system are not comparable, since these are to be regarded as parts of mechanisms for controlling different functions. The centres preside over the respective functions, but the functions themselves are not located in the centres.

[2] Boveri, "Ein Geschlechtlich erzeugter Organismus ohne Mütterliche Eigenschaften," *S. B. d. Ges. f. Morph. u. Phys., München*, vol. v., 1889.

Hickson has remarked that if it be true that the chromosomes are the sole carriers of heredity it seems to be necessary to believe in the individuality of the chromosomes; that is to say, that the chromosomes seen at the poles of the spindle at the termination of mitosis are individually identical with those seen at the equator of the spindle at the next mitosis. He points out, further, that there is distinct evidence that this is not the case in certain Protozoa and Cœlenterata. Again, Hickson has called attention to the long duration of the period of conjugation in Infusoria (Heterokaryota), remarking that this is difficult to explain if we accept the view that the cytoplasm of the conjugating cells is not concerned with the transmission of hereditary characters.[5]

On the other hand, the persistence of parental chromosome groups after fertilisation in many animals, and also the evidence of heterogenous hybridisation experiments, lend considerable support to the theory of the individuality of the chromosomes, which gains more ground every year. In *Cyclops*,[6] *Crepidula*,[7] *Cryptobranchus*,[8] the two parental groups of chromosomes after fertilisation are clearly distinguishable by their size and shape. Their peculiar characteristics are retained through a number of successive cell divisions, the two sets of chromosomes being always distinguishable on the equatorial plate of the mitotic spindle. In *Echinus*, where the chromosomes number

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[1] The nuclei of such larvæ have been shown to possess only half the normal number of chromosomes; see Morgan, "The Fertilisation of Non-nucleated Fragments of Echinoderm Eggs," *Arch. f. Entwick.-Mechanik*, vol. ii., 1895.

[2] Seeliger, "Giebt es Geschlechtlicherzeugte Organismen ohne Mütterliche Eigenschaften?" *Arch. f. Entwick.-Mechanik*, vol. i., 1894.

[3] Morgan, *loc. cit.* See also Wilson, *loc. cit.*

[4] Godlewsky, "Untersuchungen über die Bastardierung der Echiniden und Crinoiden-Familie," *Arch. f. Entwick.-Mechanik*, vol. xx., 1906.

[5] Hickson, "The Physical Basis of Inheritance," *British Assoc. Reports*, Leicester Meeting, 1907, and *Trans. Manchester Micr. Soc.*, 1907. See also Fick, "Vererbungsfragen, Reduktions- und Chromosomenhypothesen," *Merkel und Bonnet's Ergeb. f. Anat. u. Phys.*, vol. xvi., 1906.

[6] Haecker, "Ueber die Selbständigkeit der väterlichen und mütterlichen Kernbestandteile während der Embryonalentwicklung von *Cyclops*," *Arch. f. Mikr. Anat.*, vol. xlvi., 1895.

[7] Conklin, "The Embryology of *Crepidula*," *Jour. Morph.*, vol. xiii., 1897.

[8] Smith (B. G.), "The Individuality of the Germ Nuclei during the Cleavage of the Egg of *Cryptobranchus*," *Biol. Bull.*, vol. xxxvii., 1919.

about thirty-six, many of these have a distinctive shape in the form of long or short pot-hooks, clubbed or V-shaped rods. According to Baltzar,[1] the same chromosomes can be identified over and over again in successive segmentation divisions, by their peculiar shape. In hybrid fishes obtained by crossing the salt-water minnow *Fundulus* with the silver-sided minnow *Menidia*, Moenkhaus[2] could distinguish the long chromosomes of *Fundulus* (which are about 2·18 μ) from the short ones of *Menidia* (which are only 1 μ in length) in all the segmentation divisions. Morris[3] even claims that in the cross between *Fundulus* and the wrasse *Ctenolabrus*, the paternal and maternal portion of the chromatin can be clearly distinguished in the resting condition of the nuclei. In many other forms, as Sakamura[4] has recently shown in *Vicia*, certain of the chromosomes have definite constrictions near their end and sometimes in the middle; these constrictions appear in exactly the same position on these chromosomes in all successive cell divisions.

Verworn has objected on general grounds to the doctrine that the hereditary transmission of parental characteristics is mediated by the transference of nuclear substance only. This is what he says: "The physiological mode of thought will hardly be able to adapt itself to the idea of a single hereditary *substance*, which is localised somewhere in the cell, and transferred in reproduction. A substance that is to convey the characteristics of a cell to its descendants, before all else must be capable of life, *i.e.* must have a metabolism, and this is impossible without a connection with other substances necessary to cell-metabolism, *i.e.* without the integrity of *all* essential cell-constituents. The designation of a *single* cell-constituent as the specially differentiated bearer of heredity is wholly unjustified; the cell protoplasm is of exactly the same value in this respect as the nucleus, and we must constantly return to the fact that in all living nature no instance is known in which a complete cell possessing nucleus and protoplasm does not always mediate hereditary transmission. The character of every cell is determined by its peculiar metabolism. Hence, if the peculiarities of a cell are to be transmitted, its characteristic metabolism must be transmitted; this is only conceivable when nuclear substance and protoplasm, with their metabolic relations, are transferred to the daughter-cells. This is true of the sexual reproduction of the higher animals, as well as of the asexual reproduction of unicellular organisms; in the former, however, the metabolism of one cell, the spermatozoön, is by the process of fertilisation combined with that of another cell, the ovum, into a single resultant, the metabolism of the offspring that arises from the fertilised ovum: the offspring hence possesses the characters of the two parents."[1]

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[1] Baltzar, "Die Chromosomen von *Stronglocentrotus lividus* und *Echinus microtuberculatus*," *Arch. f. Zellforsch.*, vol. ii., 1909.

[2] Moenkhaus, "The Development of the Hybrids between *Fundulus heteroclitus* and *Menidia notatus*, with especial reference to the Behaviour of Maternal and Paternal Chromosomes," *Jour. Anat.*, vol. iii., 1904.

[3] Morris (M.), "The Behaviour of the Chromatin in Hybrids between *Fundulus* and *Ctenolabrus*," *Jour. Exp. Zool.*, xvi., 1914.

[4] Sakamura, "Experimentelle Studien über die Zell- und Kernteilung mit besonderer Rücksicht auf Form, Grosse, und Zahl der Chromosomen," *Jour. Coll. Science, Imp. Univ. Tokyo* vol. xxxix., 1920.

Morgan, in a work on the "Physical Basis of Heredity,"[2] has collected together the evidence that the chromosomes are the bearers of the hereditary factors. He states that the embryological evidence, while making out a strong case, is of itself insufficient to establish it, but taken in conjunction with the genetic evidence derived from the study of the sex chromosomes (see below, Chapter XV.) and chromosome variation forces the conclusion that this view is correct. On the other hand, Morgan recognises the occurrence of what he calls "cytoplasmic inheritance," and says that the reactions by means of which the embryo develops, and many physiological processes are maintained, reside at the time in the cytoplasm "as the embryological evidence seems to indicate." Furthermore, there is also genetic evidence to show that certain forms of inheritance are the outcome of self-perpetuating bodies in the cytoplasm, most of which go under the name of plastids. Recognition of plastid inheritance carries with it the idea that if there are such self-perpetuating materials in the cytoplasm they will have to be taken into account in any complete theory of heredity.

TELEGONY

It used to be supposed that the spermatozoa of an animal on being introduced into a female of the same kind, besides fertilising the ripe ova and producing young, were capable of exercising a permanent influence over the mother, and so transmitting certain of their characters, not only to their own immediate offspring, but to the future offspring of the mother by another sire. This phenomenon,[3] in which many practical breeders still believe, was called Telegony or Infection, and the female was said to be "infected" by the previous sire.

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[1] Verworn, *loc. cit.* *Cf.* Farmer (*loc. cit.*), who regards the chromosomes of the nucleus as representing *primordia*, which are responsible for the appearance of the hereditary characters, but need to be supplemented by *specific exciting substances* which determine what particular potential character shall actually develop.

[2] Morgan, *The Physical Basis of Heredity*, Philadelphia and London, 1920.

[3] The phenomenon was explained by supposing that the young, while still *in utero*, in some way affected the mother, and this influence was further transmitted to the subsequent offspring. It will be seen that this explanation assumes the possibility of the inheritance of acquired characters of which there is little or no evidence. For recent reviews of this question see Morgan, *Experimental Zoology*, New York, 1907; Thomson, *Heredity*, 4th Edition, London, 1920; and MacBride, *Science Progress*, vol. xv., 1921. See also below, p. 209.

The classical example, and one in which Darwin[1] himself believed, of the supposed influence of a previous sire upon the future offspring, is the case of Lord Morton's quagga, which was stated to have infected an Arab mare, so that she subsequently produced two striped colts by a black Arab horse. In recent years Ewart[2] has repeated the experiment, employing a Burchell's zebra and a number of different mares. These experiments were supplemented by others in which animals of various kinds were used. As a result of his investigations he has come to the conclusion that there is no evidence for the existence of Telegony. A microscopic examination of the structure of the hairs of the subsequent foals bred by Professor Ewart provided further negative evidence.[3] Minot,[4] also, in a series of experiments upon guinea-pigs, found no indication of any telegonic influence. Moreover, Karl Pearson,[5] as a result of an extensive statistical inquiry, was unable to discover any evidence of telegony in man.[6]

EFFECT OF EXTERNAL CONDITIONS AND OF THE SOMA ON THE GERM-CELLS

Attempts have been made by Stockard[7] and by Pearl[8] to modify the germ-cells of animals by giving alcohol by inhalation to the parents. The young produced were often degenerate, paralytic or deformed, especially the males, and the descendants of these offspring are said to have been often worse than the first generation. Similar experiments by Cole and Bachhuber,[1] in which lead was administered to male rabbits and fowls, are said to have resulted in a lowering of vitality and a decrease in size on the part of the young. Fraenkel[2] states that the young of rabbits whose ovaries were subjected to X-rays were stunted.

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[1] Darwin, *The Variation of Animals and Plants under Domestication*, Popular Edition, vol. i., London, 1905.

[2] Ewart, *The Penicuik Experiments*, London, 1899.

[3] Marshall, "On Hair in the Equidæ," *Proc. Roy. Soc. Edin.*, vol. xxiii., 1901.

[4] Minot, "An Experiment with Telegony," *British Assoc. Reports*, Cambridge Meeting, 1904.

[5] Pearson, *The Grammar of Science*, 2nd Edition, London, 1900.

[6] According to Kohlbrugge spermatozoa may penetrate the epithelium of the uterine mucosa (in the mouse, rabbit, bat, etc.), and he suggests that they may even unite with epithelial cells. These observations are advanced as a possible explanation of Telegony. (Kohlbrugge, "Der Einfluss der Spermatozoiden auf den Uterus; ein Beitrag zur Telegonie," *Zeitsch. f. Morph. und Anthrop.*, vols. xii. and xiii., 1910 and 1911.) Waldstein and Eckler maintain that the absorption of spermatozoa is proved because after coitus in rabbits the blood of the female develops a specific ferment directed against spermatozoa. (Waldstein and Eckler, "Der Nachweis resorbierten Spermas im weiblichen Organismus," *Wien klin. Woch.*, vol. xxvi., 1913.) The term "Xenia," which means guestgifts (see Thomson, *Heredity*, London, 1920), was applied by Focke to cases of plants in which the male pollen was supposed to affect the ovarian tissue (the seed's substance or the fruit) rather than the embryo itself. The term has also been applied to cases of birds where the colour of the egg laid is said to be influenced by the cock. Thus canaries crossed by siskins, linnets, or goldfinches are described by Tschermak (*Biol. Centralbl.*, 1910) as having the colour of the egg-shells modified by the male which fertilised the ova.

[7] Stockard and Papanicolaou, "Hereditary Transmission of Degeneracy and Deformities by Descendants of Alcoholised Mammals," *Amer. Naturalist*, vol. l., 1916, and *Interstate Med. Jour.*, vol. xxiii., 1916.

[8] Pearl, "On the Effect of Continued Administration of certain Poisons to the Domestic Fowl, etc.," *Proc. Amer. Phil. Soc.*, vol. lv., 1916.

Various experiments have been carried out in which ova or ovaries obtained from one animal have been transplanted into another. Thus, Heape[3] successfully inserted the segmenting ova of an Angora rabbit into the Fallopian tube of a Belgian hare, but though the young developed in the uterus of the foster-mother, there was no evidence that the latter influenced the characters of the offspring. Guthrie,[4] in experiments in transplanting the ovaries of fowls of one variety into those of another, claimed to have proved that the ova produced were influenced by the soma of the foster-parents, since (for example) a black-plumaged hen supplied by transplantation with an ovary from a white hen, when mated to a white cock gave about equal numbers of white and spotted chickens. Guthrie supposed that the black spots on the plumage of some of the chicks showed that the black foster-mother had infected the engrafted "white" eggs. Davenport,[5] who repeated the experiments, came to the conclusion that the transplanted ovaries never really became functional, and that the eggs produced were derived from regenerated ovaries that had not been completely extirpated.

On the other hand, Castle and Philips,[6] who performed similar experiments with guinea-pigs, state that the transplanted ovaries yielded eggs which were afterwards fertilised, and that the offspring were unaffected by the soma of the foster-mothers. Thus, a white guinea-pig into which an ovary from a black one was grafted, when mated to a white male, gave birth to litters of black young ones.

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[1] Cole and Bachhuber, "The Effect of Lead on the Male Germ-Cells of the Male Rabbit and Fowl, etc.," *Proc. Exp. Biol. and Med.*, vol. xii., 1914.

[2] Fraenkel, "Röntgenstrahlenversuche am tierischen Ovarien usw.," *Arch. f. Mikr. Anat.*, vol. lxxx., 1912.

[3] Heape, "On the Transplantation and Growth of Mammalian Ova within a Uterine Foster-Mother," *Roy. Soc. Proc.*, vol. xlviii., 1890, and vol. lxi., 1897.

[4] Guthrie, "Further Results of Transplantation of Ovaries in Chickens," *Jour. of Exp. Zool.*, vol. v., 1908.

[5] Davenport, "The Transplantation of Ovaries in Chickens," *Jour. of Morph.*, vol. xxii., 1911.

[6] Castle and Philips, *On Germinal Transplantation in Vertebrates*, Carnegie Institute (Washington) Publication, No. 144, 1911.

ON GAMETIC SELECTION AND THE CONDITIONS FAVOURABLE FOR THE OCCURRENCE OF FERTILISATION

It is a well-known fact in biology that, as a general rule, conjugation occurs most readily between gametes belonging to the same kind of organism. There are innumerable cases, however, in which the spermatozoa of one species are capable of fertilising the ova of another, and so initiating development. The resulting embryo in such cases may grow into a mature hybrid offspring which is not infrequently sterile (a fact which will be referred to again later), or, on the other hand, owing to some mutual incompatibility in the respective modes of growth inherited from the two parent forms, the embryo may survive for a short time and then perish.

Cross-fertilisation can usually be induced most easily among closely related species or among varieties belonging to the same species. Thus, the different varieties of the frog, *Rana fusca*, intercross as readily with one another as each variety fertilises its own ova. On the other hand, the gametes of two species as widely separate as the frog, *Rana fusca*, and the salamander, *Triton alpestris*, have been known to conjugate, but the fertilised eggs so produced divided irregularly and consequently failed to develop.[1] In some cases (*e.g.* the two species of frogs, *R. fusca* and *R. arvalis*) cross-fertilisation can take place in one direction, but not in the reverse. Pflüger explained this result by supposing it to be due to peculiarities in the shape or structure of the spermatozoa, those which have the thinnest or most pointed heads being described as more successful in inducing cross-fertilisation than those with large stout heads.[2] This explanation, while seeming to account for certain individual instances, cannot be applied to all cases of cross-sterility.

Bataillon[3] has described experiments in which he fertilised the eggs of *Pelodytes* and *Bufo* with the spermatozoa of *Triton alpestris*, and obtained some degree of success, for the eggs in each case underwent an irregular segmentation before they perished. The spermatozoa underwent degeneration after conjugating, so that the chromatin of the fertilised ova was derived entirely from the female pronucleus. The experiments, therefore, afford additional proof that spermatozoa in conjugating with ova perform a function altogether apart from amphimixis (or the introduction of fresh chromatin substance as a source of variation), and that this function is the initiation of development.

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[1] Pflüger, "Die Bastardzeugung bei den Batrachiern," *Pflüger's Archiv*, vol. xxix., 1882.

[2] Pflüger and Smith, "Untersuchungen über Bastardierung der Anuren Batrachier, etc.," *Pflüger's Archiv*, vol. xxxii., 1883.

[3] Bataillon, "Impregnation et Fécondation," *C. R. de l'Acad. des Sciences*, vol. cxlii., 1906.

Among the Mammalia, as is well known, cross-fertilisation between nearly allied species commonly occurs. The resulting hybrid may be either sterile (*e.g.* the mule) or fertile (*e.g.* the hybrid offspring of the bull and American bison). There is no evidence that more widely separated species of Mammals can be induced to have hybrid offspring. Spallanzani,[1] by artificially inseminating an œstrous bitch with the spermatozoa of a cat, attempted such an experiment, but without a positive result.

A number of investigators have effected cross-fertilisation between various kinds of Echinoderms. Vernon,[2] who experimented with forty-nine different combinations, obtained results which were more or less successful in thirty-seven. In some of these, however, development did not proceed beyond the blastula stage. Vernon attempted to show that the capacity of the animal to transmit its characters to its hybrid offspring depended upon the condition of ripeness or staleness of its gametes at the time of fertilisation. Thus, the spermatozoa of the sea-urchin, *Strongylocentrotus*, were supposed to grow more and more "prepotent" as they became more and more mature. Doncaster,[3] however, has described further experiments which seem to indicate that the variation in the form of the hybrids obtained by Vernon was really due to differences in the temperature of the water.

Shearer, de Morgan, and Fuchs[4] have been able to obtain an F_2[5] generation from the cross *Echinus esculentus* ♀ × *E. acutus* ♂ at Plymouth, but were unable to obtain fertile individuals of the cross *E. miliaris* ♀ × *E. esculentus* ♂ or *E. miliaris* ♀ × *E. acutus* ♂ although fairly large and healthy F_1 individuals of both these crosses were reared. In all instances the gonads of the F_1 crosses with *E. miliaris* failed to develop beyond a very rudimentary condition. As the result of extensive investigation of the early larval characters, these authors come to the conclusion that they are too variable to afford any trustworthy evidence of parental influence. This is particularly so with regard to the skeleton, which has been used so extensively by previous workers in this subject. In the late larval life, characters such as the posterior ciliated epaulettes or ciliated rings are ones that show very little variation and to which no exception can be taken. *E. esculentus* and *E. acutus* always develop the posterior ciliated epaulettes while *E. miliaris* never possess these structures. In crosses between these forms conducted over three years, maternal inheritance with regard to this character was invariably observed, the reciprocals of a cross being unlike. In the fourth year's work, however, the inheritance of this character proved different and gave a dominance of *E. esculentus* and *E. acutus* over *E. miliaris*, both reciprocals of a cross being alike. No reason for this change could be suggested. The cytological study of material of all the crosses during the course of the work showed that in all instances true fusion of the pronuclei during fertilisation took place, but varying amounts of chromatin were thrown out of the nuclei in different crosses and in different experiments.

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[1] Spallanzani, *Dissertations*, English Translation, vol. ii., London, 1784.

[2] Vernon, "The Relation between the Hybrid and Parent Forms of Echinoid Larvæ," *Phil. Trans.*, B., vol. cxc., 1898.

[3] Doncaster, "Experiments in Hybridisation," *Phil. Trans.*, B., vol. cxcvi., 1903. MacBride ("Some Points in the Development of *Ophiothrix fragilis*," *Proc. Roy. Soc.*, B., vol. lxxix., 1907) has recently shown that the immature (ovarian) ova of the Ophiuroid, *Ophiothrix*, may be fertilised, but that the subsequent development is abnormal, segmentation resulting in a morula instead of a blastula, while at the stage at which the archenteron is formed, there is a tongue of cells projecting into its lumen. It appears, therefore, that the stage of maturity at which ova are fertilised may affect their embryonic development if not their hereditary characteristics.

[4] Shearer, de Morgan, and Fuchs, "On the Experimental Hybridisation of Echinoids," *Phil. Trans. Roy. Soc. Lond.*, Ser. B., vol. cciv., 1914. See also H. M. Fuchs, *Jour. Mar. Biol. Ass.*, vol. x., 1914.

[5] See footnote, p. 202.

Loeb[1] discovered that cross-fertilisation of the eggs of *Strongylocentrotus* by the spermatozoa of various species of starfish could be effected by adding sodium carbonate or sodium hydroxide to the sea-water in just sufficient quantity to render it slightly alkaline. Under these conditions as many as fifty per cent. of the *Strongylocentrotus* eggs could be fertilised by *Asterias* spermatozoa, whereas in normal sea-water cross-fertilisation between these two Echinoderms only occurs very exceptionally. What the nature of the change is whereby the alkaline sea-water enables the sperm to fertilise the ova does not appear to be known. It has been observed that the addition of the alkali increases the motive power of the sperms, but the same result is brought about by bicarbonate of sodium, without augmenting their capacity to cross-fertilise. Loeb suggests that the entrance of the spermatozoön into the interior of the egg-protoplasm may be due to surface-tension forces, and that the conditions for this process may depend upon the surface tension between the spermatozoön and the sea-water becoming greater than the sum of the surface tensions between the sea-water and the egg, and the spermatozoön and the egg. Loeb remarks, further, that the fertilisation of *Strongylocentrotus* eggs by sperms of the same species can best be accomplished in normal sea-water, and with this observation he associates the fact that the mobility of the *Strongylocentrotus* sperms is diminished by the alkaline water.[2]

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[1] Loeb (J.), "Ueber die Befruchtung von Seeigeleiern durch Seesternsamen," *Pflüger's Archiv*, vol. xcix., 1903. "Weitere Versuche über heterogene Hybridisation bei Echinodermen," *Pflüger's Archiv*, vol. civ., 1904. See also translation of the latter, as well as other papers, in the University of California Publications, *Physiology*, vols. i. and ii., 1902-4.

[2] Loeb, *The Dynamics of Living Matter*, New York, 1906.

While suggesting that restrictions to the power of cross-fertilisation may be due to differences in surface tension, Loeb admits that the evidence seems to show that the capacity to conjugate is to some extent at least specific. Attempts were made to fertilise the eggs of sea-urchins with the spermatozoa of Annelids and Molluscs, but these experiments were without success. Kupelweiser,[1] however, reports that he has been successful in fertilising *Strongylocentrotus* ova with the spermatozoa of the mussel (*Mytilus*), and that the products developed into gastrulæ.

Gray[2] finds that the spermatozoa of *Echinus miliaris* in sea-water are affected by positive trivalent ions such as those of Ce and La, in much the same way as colloidal particles of albumen and globulin. It is only those solutions that are capable of maintaining the normal negative charge on the sperm unaltered that allow vigorous movement of the sperm. Trivalent positive ions flocculate sperm suspensions by lowering this negative charge. The action of $H^{\cdot}$ is very intense and changes the surface charge on the sperm from negative to positive without any intermediate flocculation. The work of Teague and Buxton[3] shows that living cells (bacteria) are much more sensitive to flocculation than dead cells or mastic particles. Girard and Audubert[4] claim that bacteria owe most of their biological properties, such as viability, pathogenetic power, etc., to their surface charge.[5] In the same way Gray suggests that the action of $H^{\cdot}$-ion in bringing about the various effects found in heterogenous hybridisation experiments is to be explained by the action of this ion on the membrane charge of eggs and sperm. If sperm are placed in sea-water to which a certain amount of acid is added, their surface charge is reduced considerably below normal. Eggs put in the same solution will have their charge altered to a different degree, and thus the results of heterogenous hybridisation could be explained in a simple manner.

Dr. A. T. Masterman tells me that, in certain cases, hybridisation among fishes may be induced more readily in the absence of opportunity for normal fertilisation, that is to say, for fertilisation of ova by spermatozoa of the same species. If such ova are present the spermatozoa tend to conjugate with them rather than with ova belonging to a different but closely allied species. It would appear, therefore, that the spermatozoa exhibit an elective affinity for ova belonging to the same species as themselves. This has been shown especially in hybridisation experiments between brill and turbot.[1]

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[1] Kupelweiser, "Versuche über Entwickelungserregung und Membranbildung bei Seeigeleiern durch Molluskensperma," *Biol. Centralbl.*, vol. xxvi., 1906.

[2] Gray (J.), "The Relation of Spermatozoa to Certain Electrolytes," II., *Proc. Roy. Soc. Lond.*, Ser. B., vol. xci., 1920.

[3] Teague and Buxton, "Die Agglutination in Physikalischen Hinsicht," III., *Zeitsch. f. Physikal. Chem.*, vol. lvii., 1906.

[4] Girard and Audubert, "Les charges électrique des microbes et leur tension superficielle," *Compt. Rend. Acad. Science*, vol. clxvii., 1918.

[5] In the case of an asporogonous strain of Anthrax, the reduction of the normal charge of the double electric layer (σd) from a value of $3{\cdot}68$ to $2{\cdot}47 \times 10^{-6}$ C.G.S., quintuples the normal growth of the culture, while by the reduction of the value of σd to 0, many pathogenetic bacteria are rendered harmless.

That assortative mating amongst gametes occurs generally as the result of a preferential tendency possessed by them towards conjugating with other gametes bearing similar characters to their own, and that the comparative scarcity of hybrids in a state of nature is very largely the result of this selective action, are facts with which many of the older naturalists were familiar. With reference to the various species of plants belonging to the family Compositæ, Darwin wrote as follows:—

"There can be no doubt that if the pollen of all these species could be simultaneously or successively placed on the stigma of any one species, this would elect with unerring certainty its own pollen. This elective capacity is all the more wonderful as it must have been acquired since the many species of this great group of plants branched off from a common progenitor."

Romanes,[2] who quotes this passage, remarks that "Darwin is here speaking of 'elective affinity' in its fully developed form, as absolute cross-sterility between fully differentiated species. But we meet with all lower degrees of cross-infertility—sometimes between 'incipient species,' or permanent varieties, and at other times between closely allied species. It is then known as 'prepotency'[3] of the pollen belonging to the same variety or species over the pollen of another variety or species, when both sets of pollen are applied to the same stigma. Although in the absence of the prepotent pollen the less potent will fertilise the seed, yet, such is the appetency for the more appropriate pollen, that even if this be applied to the stigma some considerable time after the other, it will outstrip or overcome the other in fertilising the ovules, and therefore produce the same result on the next generation as if it had been applied to the mother plant without any admixture of the less potent pollen, although in some cases such incipient degrees of cross-infertility are further shown by the number or quality of the seeds being fewer or inferior."

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[1] M'Intosh and Masterman, *Life History and Development of the Food Fishes*, and articles in the *Reports of the Scottish Fishery Boards*, 9th Rep., Pt. III., 10th Rep., Pt. III., and 13th Rep., Pt. III.

[2] Romanes, *Darwin and After Darwin*, vol. iii., London, 1897. See also Darwin, *Animals and Plants*, London, 1875, and *Cross- and Self-Fertilisation in Plants*, London, 1876.

[3] The term "Prepotency" is here used in a different sense to that in which it is usually employed by zoologists, according to whom it means the greater capacity of one parent, as compared with the other, to transmit its characters to its offspring; thus, instead of both parents transmitting their characters equally, one may be "prepotent" over the other. (*Cf.* the Mendelian term "dominant," which has a more precise signification; see p. 199.)

It would appear, however, that when the aggregate vitality of the ova and spermatozoa is reduced below a certain point, assortative mating as a result of affinity between gametes bearing similar characters no longer occurs. It thus happens that a reduction of vitality is frequently correlated with an increased tendency towards cross-fertilisation, which, on this view, is a source of renewal of vitality. This theory was adopted to explain certain phenomena of cross-fertilisation occurring among plants, by Fritz Müller, who wrote as follows:—

"Every plant requires for the production of the strongest possible and most prolific progeny, a certain amount of difference between male and female elements which unite. Fertility is diminished as well when this degree is too low (in relatives too closely allied) as when it is too high (in those too little related)." And, further, "species which are wholly sterile with pollen of the same stock, and even with pollen of nearly allied stocks, will generally be fertilised very readily by the pollen of another species. The self-sterile species of the genus *Abutilon*, which are, on the other hand, so much inclined to hybridisation, afford a good example of this theory, which appears to be confirmed also by *Lobelia*, *Passiflora*, and *Oncidium*."[1]

Castle[2] found that the eggs of the hermaphrodite Ascidian, *Ciona intestinalis*, could not, as a rule, be fertilised by spermatozoa derived from the same individual, while they could be fertilised readily with the spermatozoa of another individual. This rule, however, was not without exceptions, for in some cases as many as fifty per cent. of the eggs of one *Ciona* could be fertilised with sperms of the same individual, although this was very unusual. Morgan, who confirmed Castle's observations, states that the failure to conjugate is due to the inability of the sperms to enter the eggs. If the sperm succeeds in entering, as in the exceptional cases, the fertilised egg develops normally. Morgan found, further, that if the sperms are stimulated to greater activity by alcohol, ether, ammonia, or certain salt solutions, self-fertilisation may in some cases be induced. In another Ascidian, *Cynthia partita*, Morgan observed that self-fertilisation frequently occurs, but that the eggs in this species also are most usually fertilised by spermatozoa from another individual.[3] The foregoing results of Castle and Morgan have been repeated by Fuchs,[1] who finds that, in *Ciona*, the self-fertilisation rate can be greatly increased if concentrated sperm suspensions are employed. This rate can also be much increased if a little egg extract is added to the sea-water in which the fertilisation is carried out. The presence of the egg extract has an immediate effect in raising the fertilisation percentage. Extract of ovary or blood acts in the same way, the movements of the sperm being greatly stimulated. The sperm of the sea-urchin *Strongylocentrotus* is stimulated in the same manner by egg extract of its own eggs or those of *Sphærechinus*, *Echinus*, or *Ciona* eggs, but *Asterias* egg extract completely inhibits the fertilising power of a *Strongylocentrotus* sperm suspension. Fuchs has shown that a small rise in the H-ion concentration of the sea-water brings about much the same effect as the addition of egg extract, and, as a matter of fact, the addition of egg extract to normal sea-water caused a slight rise in its H-ion concentration.

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[1] Müller, "Investigations respecting the Fertilisation of *Abutilon*," English Translation in *American Naturalist*, vol. viii., 1874.

[2] Castle, "The Early Embryology of *Ciona intestinalis*," *Bull. Mus. Comp. Zool.*, vol. xxvii., 1896.

[3] Morgan, "Self-Fertilisation induced by Artificial Means," *Jour. of Exp. Zool.*, vol. i., 1904. "Some Further Experiments on Self-Fertilisation in *Ciona*," *Biol. Bull.*, vol. viii., 1905.

Cohen[2] has shown that in sea-water in which the H-ion concentration has been slightly raised above the normal, the life of the sperm is greatly prolonged, and they are able to fertilise a greater number of eggs.

It is well known that the fertility of animals which are much in-bred is often reduced, but this is by no means invariably the case.[3] Thoroughbred horses are notoriously in-bred, and it is interesting to note that one of the earlier Reports of the Royal Commission on Horse-breeding states that no less than forty per cent. of the thoroughbred mares in this country fail to have foals each year. This relatively large amount of sterility is probably due to a variety of causes, and not entirely to the result of in-breeding.[4]

Low[5] has recorded an experiment on the effect of in-breeding in fox-hounds. The particular strain is described as having perished completely. Low states also that similar experiments have been performed upon pigs, and, as a consequence, the litters became diminished in size and frequency, while difficulty was often experienced in rearing those which were produced.

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[1] Fuchs (H. M.), "Studies in the Physiology of Fertilisation," *Jour. Genetics*, vol. iv., 1915.

[2] Cohen (E. J.), "Studies in the Physiology of Spermatozoa," *Biol. Bull.*, vol. xxxiv., 1918.

[3] The results of in-breeding are discussed at some length by Darwin, *Variation of Animals and Plants*, vol. ii., Popular Edition, London, 1905. For reviews of the subject see Morgan, *Experimental Zoology*, New York, 1907; and East and Jones, *In-breeding and Out-breeding*, Philadelphia and London. Pearl has worked out a mathematical formula for estimating the degree of in-breeding, *Amer. Nat.*, vol. xlvii., 1913.

[4] Returns obtained by the Ministry of Agriculture show about the same degree of fertility for cross-bred mares served by Shire stallions.

[5] Low *The Domesticated Animals of Great Britain*, London, 1845.

Von Guaita,[1] and Bos,[2] in describing the effects of in-breeding in mice and rats respectively, have recorded a steady decrease of fertility in successive generations.

King,[3] on the other hand, found no reduction in the fertility of rats in-bred, for twenty-five successive generations, by brother and sister mating.[4]

Castle and his collaborators,[5] as a result of an investigation upon the same question in the pumice-fly (*Drosophila ampelophila*), have come to the conclusion that in-breeding tends to reduce the fertility to a slight extent, whereas cross-breeding has a contrary effect. The experiments showed further that in-breeding results in strains of unequal fertility. The less fertile were eliminated by the productiveness being differential, so that only the more fertile persisted. Moreover, whereas complete sterility was marked in the first part of the experiment, in the later generations it has almost completely disappeared. Moenkhaus,[6] and others, in similar experiments on in-breeding *Drosophila*, found likewise that though sterility increased in the earlier generations the later ones were fertile.

East[7] interprets these results on the hypothesis that in-breeding produces homozygous individuals (to use Mendelian terminology) and that these when sterile are eliminated. He illustrates his conclusions by reference to experiments on maize in which in-breeding produces different results in different lines, showing that segregation of certain factors influencing fertility has taken place.

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[1] Von Guaita, "Versuche mit Kreuzungen von verschiedenen Rassen der Hausmaus," *Ber. d. Naturf. Gesell.*, Freiburg, vol. x., 1898.

[2] Bos, "Untersuchungen ueber die Folgen der Zucht in engster Blutverwandtschaft," *Biol. Centralbl.*, vol. xiv., 1894.

[3] King, "Studies in In-breeding," *Jour. of Exp. Zool.*, vol. xxvi., 1918.

[4] Westermarck attributes the practice of exogamy (or marriage outside the clan or family) in man to an instinctive aversion to marriage and sexual intercourse between persons who have lived together closely through early youth, and this mental characteristic is supposed to have arisen through natural selection in view of the needs of the species which would suffer as a result of in-breeding. In this theory Westermarck correlates "three parallel groups of facts . . . the exogamous rules, the aversion to sexual intercourse between persons living together from childhood, and the injurious consequences of in-breeding" (*The History of Human Marriage*, 5th Edition, in three volumes, London, 1921). Heape has a different theory of the origin of exogamy, attributing it to the instinct which impels the errant male to seek a strange female for his sexual gratification, and points out that when the pair are not in accord the sexual stimulus for ovulation may not occur (*Sex Antagonism*, London, 1913. See also Frazer, *Totemism and Exogamy*, London, 1911).

[5] Castle, Carpenter, Clark, Mast, and Barrows, "The Effects of In-breeding, etc., upon the Fertility and Variability of *Drosophila*," *Proc. Amer. Acad. of Arts and Sciences*, vol. xli., 1906.

[6] Moenkhaus, "The Effects of In-breeding and Selection on Fertility, Vigor, and Sex Ratio on *Drosophila*," *Jour. of Morph.*, vol. xxii., 1911.

[7] East and Jones, *In-breeding and Out-breeding*, Philadelphia and London. This monograph contains a valuable discussion and numerous references to literature.

"Sterility in the form of structural degeneration when it occurs gradually increases upon in-breeding until homozygosity is attained, but for the most part it does not show any clear-cut segregation. Yet reduction in fertility is noticeable only so long as there is a change in other characters, constancy in visible characters being accompanied by constancy in the matter of fertility. In other words, there is no more an accumulation of sterility on continued in-breeding than there is an accumulation of any other effect. Any reduction in fertility ceases when homozygosity is reached, but the end result may be decidedly different in various lines coming originally from the same stock." In another passage East writes, "While we are not justified in concluding . . . that in-breeding accompanied by rigid selection will be beneficial [the experiments] certainly show close mating is not invariably injurious."

The diminished fertility of in-bred animals may be due partly to a decrease in the supply of mature ova perhaps correlated with a general want of vigour. It seems possible, however, that it also results from failure on the part of the gametes to conjugate, since the productiveness of in-bred animals can often be increased by cross-breeding with other varieties (see p. 639).

Heape[1] states that Dorset Horn sheep, when served by rams of their own breed, show a greater tendency towards barrenness than when served by Hampshire Down rams. It is possible that what in this case appears to be barrenness is in reality very early abortion, the in-bred embryos tending to die at an early stage and to be absorbed *in utero*, thus escaping observation.[2] It seems not unlikely, however, that, in the absence of cross-breeding, there is sometimes an insufficiency of vitality at the very outset, the elective affinity of the gametes being too feeble to induce conjugation.

Some years ago the writer carried out an experiment upon a bitch belonging to the Dandie Dinmont variety, which is known to be very in-bred. Seminal fluid was obtained from a pure-bred Dandie Dinmont dog, and also from an obviously mongrel terrier of unknown ancestry. The semen from the two dogs was examined microscopically, and in each case was found to be rich in sperms, which so far as seen were all moving and in a vigorous condition. Approximately equal quantities of each sample of semen were then mixed together in a glass tube. After a further examination of the mixture, when it was observed that all the sperms were still active, the fluid was injected into a pure-bred Dandie Dinmont bitch, which was distantly related to the Dandie Dinmont dog. Previously to the experiment the bitch had been kept apart from other dogs, and this restriction was continued so long as she showed signs of œstrus. Fifty-nine days after the injection the bitch littered four pups, which closely resembled one another. Of these one died early, but the other three grew into mongrels which somewhat resembled the terrier sire, so that there can be little doubt that all four pups were mongrels. No stress should be laid upon the result of a single experiment; but the evidence, such as it was, was indicative of a selective tendency, consequent upon a reduced vitality, on the part of the ova of the in-bred animal to conjugate with dissimilar rather than with related spermatozoa.

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[1] Heape, "Abortion, Barrenness, and Fertility in Sheep," *Jour. Royal Agric. Soc.*, vol. x., 1899.

[2] Hammond ("On Some Factors Controlling Fertility in Domestic Animals," *Jour. of Agric. Science*, vol. vi., 1914), who has described the common occurrence of degenerative fœtuses in the uterus of the sow, suggests that this may be the result of "lethal factors" intensified by in-breeding in the manner postulated by East. Kirkham ("Embryology of Yellow Mouse," *Proc. Amer. Soc. Zool.*, *Anat. Record*, vol. xi., 1917) and Ibsen and Steigleder ("Evidence of the Death *in utero* of the Homozygous Yellow Mouse," *Amer. Nat.*, vol. li., 1917) have supposed that homozygous yellow mice, which are never born, but seem invariably to die in the uterus, carry a "lethal factor."

Professor Ewart has informed the writer of a case in which a Dandie Dinmont bitch in his possession copulated with a dog belonging to the same breed, and two days subsequently had intercourse with a Scotch terrier. In due time the bitch littered three pups, and of these only one was a pure-bred Dandie Dinmont, while the other two were half-bred Scotch terriers, in spite of the fact that the Dandie Dinmont dog copulated two days earlier than the Scotch terrier. This case may be regarded as to some extent confirmatory of the experiment described above.[1]

Doncaster,[2] in describing his experiments on Echinoid hybridisation, states "that cross-fertilisation is assisted by conditions which tend to reduce the vitality of the eggs." This artificial reduction of vitality could be accomplished either by warming the eggs, or by shaking them, or by keeping them for several hours, or by placing them for from one to two hours in diluted sea-water, the last method being the most uniformly conducive to the occurrence of cross-fertilisation. There is some evidence, therefore, that a reduction of vigour among the gametes, whether occurring naturally as a consequence of in-breeding or produced artificially as in Doncaster's experiments, may lead to a similar result, since both conditions may bring about an increased tendency towards the union of dissimilar gametes. On another view, the tendency towards cross-fertilisation in Doncaster's experiments may be looked upon as evidence of a diminished power of resistance, on the part of the ova, to the entrance of foreign spermatozoa, consequent upon a reduced vitality in the ova.[1]

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[1] Seeing that an assortative mating of gametes can probably occur between the ova of one individual and the spermatozoa derived from different individuals, whether as a result of gametic similarity or reduction of vitality, it is not improbable that gametic selection also sometimes takes place when various gametes of a single individual are bearers of different characters, in the manner postulated by the Mendelian theory. Such a preferential mating, if it exists, would of course obscure the evidence of that very gametic segregation, the probable existence of which, in other cases, is inferred from the numerical proportions in which the different sorts of zygotes or offspring are produced; for if there is an assortative mating among the gametes, it is obvious that the offspring would no longer be produced in definite Mendelian proportions, since these depend upon the chance unions of gametes. According to this view, prepotency may perhaps be interpreted as the tendency of the gametes of an individual to conjugate with other gametes bearing similar hereditary characters.

[2] Doncaster, *loc. cit.*

Further evidence upon this question is afforded by studying the Protozoa (see also pp. 639-642).

CONJUGATION IN THE PROTOZOA

The phenomenon of conjugation in the Protozoa possesses a special interest, inasmuch as it is undoubtedly the forerunner of fertilisation in the Metazoa. It is clear, therefore, that a complete understanding of the changes which attend the former process cannot fail to throw great light on the nature and significance of gametic union in multicellular organisms.

In the different groups of Protozoa all gradations are to be found between the conjugation in the general sense (*i.e.* the union, either temporary or permanent, of two similar unicellular organisms), and a process identical with metazoan fertilisation. Thus, in the peritrichous Ciliata there is a pronounced sex differentiation in the size and activity of the gametes, which clearly correspond to ova and spermatozoa. Even the maturation phenomena, which play so important a part in the developmental history of the metazoan gametes, are represented in some sort by comparable processes which have been observed in certain Protozoa.[2] There can be no doubt, therefore, as to the essential similarity of conjugation in unicellular organisms and fertilisation in multicellular ones.

Raymond Pearl,[3] as a result of a biometrical study of the process of conjugation in *Paramœcium caudatum*, has arrived at the conclusion that in this protozoön there is a definite tendency for like individuals to mate with like, since there is a considerable degree of homogamic correlation both between the lengths of the conjugant pairs and also between their breadths. Evidence is presented to show that the homogamic correlation arises through the necessity for the anterior ends and mouths of the two individuals to "fit" reasonably well in the act of successful conjugation. If this is so, the necessity for assortative mating in *Paramœcium* is purely mechanical, and the principle involved is not of general application to other gametic organisms. Pearl states, also, that there is no evidence that conjugation tends to produce increased variability in ex-conjugants. On the contrary, there are indications that conjugation tends to restrict the existing variability induced by environmental influences; or, in other words, to preserve a relative stability of typè. This conclusion is antagonistic to Weismann's hypothesis referred to above (see footnote, p. 198).

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[1] It may be mentioned also that Loeb has shown that, whereas mature starfish eggs soon die if fertilisation is prevented, eggs in which maturation is artificially hindered through lack of oxygen or the addition of an acid to the sea-water, remain alive much longer than when allowed to become mature. (Loeb, "Maturation, Natural Death, and the Prolongation of the Life of Unfertilised Starfish Eggs, etc.," *Biol. Bull.*, vol. iii., 1902.) It would appear, therefore, that the mature eggs have suffered a loss of vitality which ordinarily can only be increased by the act of fertilisation.

[2] See Enriques, *loc. cit.* See footnote, p. 198.

[3] Pearl, "A Biometrical Study of Conjugation in *Paramœcium*," *Biometreika*, vol. v., 1907.

As already mentioned, the reproductive processes in the Protozoa, like those in the Metazoa, tend to run in cycles, each cycle beginning and ending with an act of conjugation. Maupas' observations showed that in various genera of Infusoria (*Paramœcium, Stylonychia*, etc.) a long period, during which the animals multiply by simple cell division, is succeeded by a period when conjugation is of very common occurrence. This marks the commencement of a new cycle, being physiologically comparable to the period of sexual maturity in multicellular organisms. If conjugation were prevented from occurring, the individuals gradually ceased to divide and underwent changes which invariably led to death. As a result of these experiments, Maupas arrived at the conclusion that the purpose of conjugation is to counteract the tendency towards senile degeneration, and to bring about a rejuvenescence or renewal of vitality.[1]

Maupas' observations have been confirmed by Joukowsky[2] and Simpson,[3] and more particularly by Calkins.[4] The last investigator found, further, that the periodic seasons of "depression" or loss of vitality which invariably occurred if conjugation were prevented, and which normally resulted in the cessation of cell division and ultimately in death, could be tided over and the race carried through further cycles of activity by having recourse to artificial stimuli in the medium surrounding the culture. In a series of experiments, which Calkins conducted for twenty-three months with a single race of *Paramœcium*, it was found that periodic reductions of vitality occurred at intervals of about six months. At such times the race under cultivation would have died out entirely had it not been for the application of stimuli in the form of extracts of various food substances (beef, pancreas, brain, etc.). With the assistance of these restoratives, on three separate occasions, this particular race of *Paramœcium* was carried through four cycles of activity and 742 generations without the occurrence of conjugation. It thus appears that a change in the environment may result in a rejuvenescence of the race.

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[1] Maupas, "Recherches expérimentales sur la Multiplication des Infusories Ciliés," *Arch. de Zool. Exp. et Gen.*, vol. vi., 1888. "Le Rajeunissement Karyogamique chez les Ciliés," *Arch. de Zool. Exp. et Gen.*, vol. vii., 1889.

[2] Joukowsky, "Beiträge zur Frage nach den Bedingungen der Vermehrung und des Eintrittes der Konjugation bei den Ciliaten," *Verh. Nat. Med. Ver.*, Heidelberg, vol. xxvi., 1898.

[3] Simpson (J. Y.), "Observations on Binary Fission in the Life-History of the Ciliata," *Proc. Roy. Soc. Edin.*, vol. xxiii., 1901.

[4] Calkins, "Studies on the Life-History of Protozoa," IV., *Jour. of Exp. Zool.*, vol. i., 1904. References to earlier papers are here given. See also *Biol. Bull.*, vol. xi., 1906, and *Amer. Nat.*, vols. xlix. and l., 1915 and 1916.)

As a consequence of these experiments, Calkins has suggested that the purpose of conjugation may be to bring about the union of individuals which have lived in different environments, and so to produce a renewal of vitality in the same kind of way as a change in the environment itself.

Calkins differs from Maupas in stating that diverse ancestry is not essential in order that conjugation may occur, since he obtained as large a percentage of successful endogamous as exogamous pairings, and carried one endogamous ex-conjugant through 379 generations. On the other hand, there is some evidence that conjugation does not result in rejuvenescence when both gametes have lived for a long time in the same medium, so that their chemical composition is too similar.[1]

According to Enriques, however, conjugation in *Colpoda steini* only takes place under certain environmental conditions (*e.g.* if the layer of the water is not thicker than two millimetres) and does not occur at all if the conditions of life are stationary, the infusorians going on multiplying indefinitely and the number of divisions from the last conjugation making no difference.[2] According to Woodruff,[3] on the other hand, a varied environment seemed to obviate the necessity for conjugation in *Paramœcium*.

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[1] Cull, "Rejuvenescence as a Result of Conjugation," *Jour. of Exp. Zool.*, vol. iv., 1907. Blackman ("The Nature of Fertilisation," *British Assoc. Reports*, York Meeting, 1906) is of opinion that the rejuvenescence theory of fertilisation is difficult to apply generally in view of the large number of plants in which the fusing cells or nuclei are closely related. The force of this objection must be admitted. If, however, the conjugating cells have been subjected to slightly different environmental influences, this near relationship is not necessarily a difficulty.

[2] If water from a culture in which conjugation is "epidemic" be added to a normal culture, it is stated to induce conjugation. Conversely, if water from a normal culture is added to a "conjugation culture" it inhibits it.

[3] Woodruff, "The Life-Cycle of *Paramœcium* when Subjected in Varied Environment," *Jour. of Exp. Zool.*, vol. xlii., 1908. Jennings, "The Effect of Conjugation in *Paramœcium*," *Jour. of Exp. Zool.*, vol. xiv., 1913.

He was able by continually altering the character of their food, and imitating the conditions of pond life, to continue the life of a single race of *Paramœcium* for over five years, and carry it through 3000 generations by simple fission without conjugation taking place.[1] Many of these cultures showed periods of depression followed by periods of increased fission, and further investigation showed that each period of depression and restoration was accompanied by a special process of nuclear reorganisation which apparently replaced the act of conjugation. The macronucleus breaks up and disappears, the micronuclei dividing twice, but do not complete the third division, which in conjugation gives rise to the gametic nuclei. A new macronucleus is formed from the micronuclei, and the normal nuclear organisation re-established in this way. To this process of nuclear reorganisation Woodruff has applied the name of "*endomixis*." The question of endomixis has been studied by Erdmann,[2] who comes to the conclusion that new lines of *Paramœcium* originate after this process, and are made constant by selection; that is, heritable variations occur in asexually conducted lines, and that the rigid conception of the ganotype does not hold true for Protozoa. If a pure line of *Paramœcium* is transferred to new environmental surroundings, it answers immediately to this change by the production of endomixis. The necessary opportunity is then given for the survival of those individuals of the new stock in equilibrium with their new surroundings. This process is constantly taking place in nature, for if a roadside pool partially dries up, or a heavy fall of rain takes place, its chemical character may be altered, but the *Paramœcia* inhabiting the pool are enabled to adjust themselves to the change through the process of endomixis.[3]

It may seem a far cry from the Ciliate Infusorian to the British thoroughbred horse, yet there is evidence that here also an in-bred and relatively infertile race may be rejuvenated through access to new surroundings. Allison, referring to blood stock of British origin, born in Australia and New Zealand, writes as follows: "We can draw from these, not only strains of blood which we have lost, but horses and mares, born again, so to speak, and admirably suited to strengthen and regenerate our home stock."[1] The same result is said to have been achieved in the descendants of British horses (especially Hackneys) imported into Argentina.[2]

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[1] Woodruff, "Rhythms and Endomixis in Various Races of *Paramœcium aurelia*," *Biol. Bull.*, vol. xxxiii., 1917; see also Woodruff and Erdmann, "Abnormal Periodic Reorganisation Process without Cell-Fusion in *Paramœcium*," *Jour. of Exp. Zool.*, vol. xvii., 1914; and Jennings, *loc. cit.*

[2] Erdmann, "Endomixis and Size Variations in Pure Bred Lines of *Paramœcium aurelia*," *Arch. f. Entwick. d. Organism*, vol. xlvi., 1920.

[3] Mr. Saunders informs me that in England roadside pools frequently undergo great changes of H·-ion concentration after rain storms.

The case of the Porto Santo rabbits and that of the goats of Juan Fernandez, which are cited by Huth[3] as evidence that in-breeding is harmless, may perhaps be similarly explained.

Moreover, such an interpretation is not necessarily inconsistent with the genetic explanation given by East and Jones (see above, p. 218), according to whom the infertility may be due to adverse factors in certain strains, since the environment may exercise an effect on the germ-plasm through the body cells and so produce a selective influence.

It would seem on the whole that the only feature common to conjugation or fertilisation throughout the animal kingdom is biparental inheritance. The association of fertilisation or conjugation with reproduction is not an essential one; as it is not universal it can hardly be a necessary relationship. In *Paramœcium*, as we have just seen, nuclear reorganisation can bring about a fresh cycle of fission equally as well as conjugation. In the higher phyla of the animal kingdom the close association of fertilisation with reproduction has completely obscured their primitive relationships and significance.

THE SUPPOSED CHEMOTACTIC PROPERTIES OF SPERMATOZOA AND THEIR RELATION TO THE PHENOMENA OF FERTILISATION

It has been suggested that the spermatozoön is attracted towards the ovum by a chemotactic action which the metabolic products of the latter are able to exert upon the former. Pfeffer's experiments[4] upon the spermatozoa of ferns are usually cited as evidence of this view.

Pfeffer observed that malic acid, when put into a capillary tube with one end open and placed in a drop of liquid containing fern spermatozoa, has a strong attractive influence upon these organisms, causing them to swim in large numbers into the opening of the tube. He concluded, therefore, that it is the malic acid in the archegonium of the fern's ovum which causes the approach of the spermatozoa.

According to Strasburger,[5] the ova of the Fucaceæ also possess chemotactic properties, attracting the spermatozoa from a distance equal to about two diameters of an ovum. Bordet,[1] however, who likewise experimented upon the Fucaceæ, obtained no evidence of chemotactic attraction, but he found, on the other hand, that the sperms were very sensitive to contact.

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[1] Allison, *The British Thoroughbred Horse*, London, 1901.

[2] Wallace (R.), *Argentine Shows and Livestock*, Edinburgh, 1904. *Cf.* also Darwin, *Animals and Plants*, London, 1905.

[3] Huth, *The Marriage of Near Kin*, 2nd Edition, London, 1887.

[4] Pfeffer, "Locomotorische Richtungsbewegungen durch chemische Reize," *Untersuchungen aus. d. Bot. Inst. zur Tübingen*, vol. i., 1884.

[5] Strasburger, *Das botan. Prakticum*, Berlin, 1887.

Jennings,[2] in the course of his experiments on the behaviour of the Protozoa, has shown that these organisms will tend to collect in a drop of acid placed in water. This is due to the fact that, whereas no reaction takes place when the individuals pass from water to acid, there is a distinct reaction in passing in the reverse direction. All the organisms which enter the drop of acid remain there, and consequently they accumulate, but this is not due to any attractive influence on the part of the drop. It is of course possible that Pfeffer's observations on the supposed attraction possessed by malic acid for the spermatozoa of ferns is susceptible of a similar explanation.

Buller,[3] who has discussed the question at some length and has performed numerous experiments, states that, so far as he is aware, not a single case is known where chemotaxis plays a part in the fertilisation of the ova of animals.

Child's Theory of the Life Cycle[4]

Child,[5] as the result of some twenty years' study of the process of regeneration in many animals, and especially with regard to Planarians, has brought forward a theory of the life cycle in plants and animals, which is of remarkable interest on account of its many applications. In this theory an attempt has been made to break away completely from the corpuscular conception of the development and inheritance of the organism, which in the past thirty years has dominated all our outlook on this subject. In the following remarks this theory can only be considered in relation to the origin of the gametes, fertilisation, and the problem of the life cycle, very briefly.

In the animal kingdom there are two well-established means of reproduction, which in many groups such as the Hydromedusæ alternate with one another, or entirely replace each other, as in some of the lower worms. First, we have asexual reproduction by fission or budding, which is usually considered the oldest form of reproduction. In some worms, such as *Planaria velata*, *Ctenodrilus monostylus*,[1] this seems to be the sole means of reproduction which these animals possess. Secondly, we have reproduction by means of gametes, and their fusion to form the zygote or fertilised egg. These two modes of reproduction are essentially similar in many respects, and one has probably been derived from the other in the course of evolution. In many Planarians, any part of the body may give rise to a new individual, provided this portion of the body becomes isolated to a certain extent, or entirely separated from the parent body. Thus *Planaria velata*, at the end of the season, breaks up into a large number of minute fragments, which contract into round spherical masses not unlike ova in appearance, and the following year give rise to new worms. The gametes or germ-cells are comparable, in Child's opinion, to these fragments of *Planaria velata*, and are therefore physiologically old cells, differing in no way from other cells of the body, except that they require conjugation with one another, in order to undergo reorganisation and rejuvenation, but still in many instances they are able to undergo this process in the absence of conjugation or fertilisation, as in parthenogenetic development. Child arrives at this conclusion as the result of a long series of investigations into the metabolic growth rate of regenerating worm fragments, and the investigation of the metabolic rate at different periods of the animal life cycle. To determine this rate certain tests are employed. In an aqueous solution of potassium cyanide or weak alcohol, in which death of the worm fragment or egg-cell occurs in from a few minutes to several hours, the susceptibility varies with the metabolic rate; thus in a fragment in which the metabolic rate is high, as shown by its consumption of oxygen, or output of CO_2, or its functional activity, the susceptibility is also very great, and all conditions which increase metabolic activity increase susceptibility. If, however, the narcotics are used in such low concentration as to admit of partial, but not complete tolerance to the new conditions, then those fragments of the worm in which growth is most rapid and the metabolic rate is highest are the last to be killed, as they have the greatest power of adjustment to the action of the narcotic. This method is the reverse of the first, and may be called the indirect susceptibility test. By the application of these tests and others of a similar character, in which potassium permanganate or phenylurethane are used, Child has shown that the growing organism possesses definite axial growth gradients, in which the metabolic rate is many times greater than in other parts of the animal. An investigation of these gradients has furnished him with information which has made possible the experimental control of morphogenesis and the development of specific form in the Planarian, perhaps the most remarkable triumph in the annals of recent biological research.

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[1] Bordet, "Contribution a l'Étude de l'Irritabilité des Spermatozoïdes chez les Fuccacées," *Bull. de l'Acad. Belgique*, vol. xxxvii., 1894.

[2] Jennings, "Studies of Reactions to Stimuli in Unicellular Organisms," *Amer. Jour of Physiol.*, vol. xxi., 1897.

[3] Buller, "Is Chemotaxis a Factor in the Fertilisation of the Eggs of Animals?" *Quar. Jour. Micr. Science*, vol. xlvi., 1902.

[4] By C. Shearer.

[5] Child's views have been put forward in *Senescence and Rejuvenescence*, Univ. Chicago Press, 1915; also in a smaller work, *Individuality in Organisms*, Chicago, 1915. To these the reader is referred for further information.

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[1] Monticelli has described a sexual phase in this animal. *Atti del Congresso dei Naturalisti italiani*, 1906, Milan, 1907.

In the Planarian, the study of these gradients shows that the metabolic processes are most active in the head region and that they diminish as we pass down the main axis of the worm, being lowest in the tail region. Those portions of the worm having the highest rate control those with a lower rate. If by transverse section we cut off the head and tail of a *Planarian*, the frequency with which it will regenerate a new head at one end x of the remaining portion of the worm, will be in direct relation to the height of the metabolic rate at this end x, and in inverse relation to the metabolic rate at the other end of the piece y. If x is higher than y, then a head will form at x, if y is higher than x, a head will form at y. If x and y have about the same metabolic rate, then we will have even chances that a head or tail will form at x or y. Now the metabolic rate at x and y can be decreased or increased at will by certain reagents, or functional activity, and so a head can be made to appear where, under less stimulation, a tail would normally regenerate, and thus the process of regeneration can be definitely controlled.

The study of the unfertilised egg-cell shows that its metabolic rate is low, and the evidence discussed in one of the foregoing sections amply testifies to this, in the astoundingly small oxygen consumption of the unfertilised egg. On fertilisaton a considerable increase of susceptibility takes place, which in *Nereis* reaches its height when the free-swimming stage is attained, while in *Arenicola* it is only reached when the young worm has developed five or six segments. In the sea-urchin *Arbacia*, and the starfish *Asterias*, the metabolic rate as determined by the direct susceptibility test reaches its highest level at the gastrula stage, and from this onwards slowly decreases, rejuvenescence comes to an end and old age begins. In Vertebrates much the same thing holds, in *Fundulus* rejuvenescence occurs during the early stages of development, but as soon as the periblast forms and the embryo assumes its shape, senescence commences. In the wrasse *Tautogolabrus*, the period of increasing susceptibility continues up to the time of hatching, and so to a much later stage than in *Fundulus*. In the frog and the salamander the average susceptibility increases from fertilisation onwards through segmentation and gastrulation to the formation of the embryo and somewhat beyond the hatching stage; after this senescence commences. The animal life cycle is therefore a more or less brief period of rejuvenescence followed by a longer and more gradual stage of senescence, in which the organism slowly grows old. Its functions come to an end through the gradual accumulation of metaplastic substances in the cytoplasm of its cells which finally bring about death. The cycle is restarted by the production of buds or germ-cells by the old organism which are capable of rejuvenescence, so the repetition of the cycle is rendered possible. It results from this conception of the life cycle that no special weight need be given to the many peculiar features connected with the origin and supposed segregation of the germ-cells, to which the Weismann theory of the germ-plasm has attached such great importance. Child has shown that in the Cestode *Moniezia*, under certain conditions, the spermatagonia can be differentiated from somatic muscle-cells, and that a germ-plasm with a given specific constitution does not hold in the case of this animal. Many of the facts of experimental embryology and regeneration, moreover, clearly render the old theory of the germ-plasm untenable. It is, however, in the explanation of those peculiar types of development in which we find pœcilogonie, pædogenesis, and dissogonie taking place that Child's theory gives us such assistance; under no other theory can these conditions be reduced to any semblance of order or meaning.[1]

In a recent paper Stockard[2] has brought forward many interesting facts that throw new light on the question of the development of specific form in animals. Thus by arresting the development of fish embryos at various stages of growth, by keeping them at low temperatures (temp. 5° C.) for a short time, definite abnormalities, such as twin or triple monsters, could be produced. There was a more or less constant relation between the abnormality produced, and the particular stage at which the embryo had been placed in the cold. An embryo kept in the cold at an early stage would subsequently, on being returned to normal temperature, develop into a twin monster; placed in the cold at a later stage of development, it would respond only by forming a double head. Lack of proper oxygen supply also brings about abnormal development in fish embryos. In Mammals, where we sometimes get polyembryony, it is suggested that an insufficient supply of oxygen to the ovum might produce this condition. The fertilised ovum travelling down the Fallopian tube probably receives an abundant supply of oxygen; arriving in the uterus in certain animals it apparently rests some time before it becomes fully implanted and the chorionic layer is formed and a free supply of oxygen from the maternal circulation is established, and such a condition might lead to polyembryony. In some animals, as the opossum and the armadillo, polyembryony would seem to be the normal mode of reproduction. In the armadillo, at least, development stops for several weeks after the blastocyst reaches the uterus, and during this time it lies perfectly free in the uterus, without any supply of oxygen from the maternal circulation.

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[1] The term *Pœcilogonie* has been introduced by Giard ("La Pœcilogonie," *VI. Congres Int. d. Zol. à Bern*, 1904) to describe that condition where an animal possesses two quite different modes of reproduction, such as that shown by the fly *Musca corvina*, which in the North of Europe reproduces by means of a large number of eggs, while in the South it is viviparous, both types of development resulting in the same adult. *Pædogenesis* is a term first introduced by von Baer (*Bull. Acad. Imp. St. Petersburg*, vol. Ix., 1866) where reproduction is carried on by the larva and not the adult, as for instance in the *Chironomus* larva, which lays eggs that give rise to a perfectly functionless adult gnat. *Dissogonie* is a term first used by Chun ("Die Dissogonie, eine neue Form der geschlechtlichen Zeugung," *Festschrift. f. Leuckart*, 1892), and describes that condition where the animal produces ripe gametes in both the embryonic or larval condition and again in the adult stage, as for example in certain Ctenophores such as *Bolina hydatina* and *Eucharis multicornis*.

[2] Stockard, "Developmental Rate and Structural Expression: An experimental study of twins, 'double monsters' and single deformities, and the interaction among embryonic organs during their origin and development," *Amer. Jour. Anat.*, vol. xxviii., 1921.

Newman[1] has brought forward in a recent book many facts of a similar character.

ARTIFICIAL AIDS TO FERTILISATION

It has been already recorded that cross-fertilisation between certain species of Echinoderms can be effected by having recourse to physico-chemical methods. It is not surprising, therefore, that fertilisation between individuals belonging to the same species can be assisted, or caused to take place more frequently, in the presence of certain substances artificially added.

Thus, according to Roux, frogs' eggs can be fertilised more readily by adding saline solution to the water in which they are deposited. Wilson says that in the case of the mollusc *Patella*, a larger number of eggs can be fertilised if potash solution is added.[2] Dungern[3] states that the activity of the spermatozoa in the sea-urchin can be increased in the presence of substances extracted from the ova. Similarly it is said that normal prostatic secretion has an exciting action on mammalian spermatozoa (p. 248). Furthermore, Torelle and Morgan[4] have shown that the immature spermatozoa of starfish can be stimulated, and fertilisation can be induced, by adding ether and various salt solutions to the sea-water (see also p. 216).

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[1] Newman, *The Biology of Twins*, Chicago Press, 1917.

[2] For further information on this subject, with references to literature, see Przibram, *Embryogeny*, English Translation, Cambridge, 1908; and Jenkinson, *Experimental Embryology*, Oxford, 1909.

[3] Dungern, "Neue Versuche zur Physiologie der Befruchtung," *Zeitsch. f. allgem. Phys.*, vol. i., 1902.

[4] Morgan, *Experimental Zoology*, New York, 1907.

PARTHENOGENESIS, NATURAL AND ARTIFICIAL[1]

The fact that the ova of various kinds of organisms are capable under certain circumstances of segmenting and developing into new individuals without the intervention of male germ-cells, has been already referred to. In such animals as the Aphidæ this method of reproduction appears to be called forth by certain conditions of temperature and moisture. In other forms of life the necessary factors for the occurrence of parthenogenesis are not so evident, but the fact of its existence has been known from early times.

In many animals parthenogenesis has been observed to occur occasionally, although it may never have become a confirmed physiological habit. The silkworm moth (*Bombyx mori*) affords an example of this phenomenon. In the higher animals also it has been shown that unfertilised eggs may very abnormally start to segment without any obvious source of stimulus. Janosik[2] has recorded segmentation in the ovarian ova of Mammals, but it is doubtful whether such cases should be regarded as truly parthenogenetic in nature.

Tichomiroff[3] showed that the unfertilised eggs of the silkworm moth, which, as just mentioned, is occasionally parthenogenetic, can be caused to develop in greatly increased numbers by rubbing them lightly with a brush, or by dipping them for about two minutes in strong sulphuric acid, and then washing them. Perez[4] subsequently made some similar observations, noting also that normal parthenogenetic development was commonest in those individuals which were most robust.

Richard Hertwig[5] was the first to show that if the ova of various Echinoderms are treated with certain reagents, and then restored to normal sea-water, they will frequently display signs of segmentation. The particular reagent originally employed by Hertwig was a 0·1 per cent. solution of sulphate of strychnine. Not long afterwards Mead[6] observed that the eggs of the marine Annelid, *Chætopterus*, which ordinarily become mature only after the entrance of the spermatozoa, could be induced to throw out their polar bodies by adding potassium chloride to the sea-water in which they were placed.

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[1] For chemistry of artificial parthenogenesis, see p. 313.

[2] Janosik, "Die Atrophie der Follikel, etc.," *Arch. f. Mikr. Anat.*, vol. xlviii., 1896.

[3] Tichomiroff, "Die künstliche Parthenogenese bei Insekten," *Arch. f. Anat. u Phys.*, Phys. Abth., Suppl., 1886.

[4] Perez, "Des Effets des Actions mécaniques sur le Développement des Œufs non-fécondés, etc.," *Procès-Verbaux de la Soc. des Sciences de Bordeaux*, 1896-97.

[5] Hertwig (R.), "Ueber Befruchtung und Conjugation," *Verhandl. der Deutsch. Zool. Gesellsch.*, 1892.

[6] Mead, *Lectures delivered at Wood's Holl*, Boston, 1898.

Morgan[1] found that an addition of sodium chloride to sea-water containing ova of sea-urchins caused these to form astrospheres, while, if the ova were afterwards transferred to ordinary sea-water, they sometimes proceeded to segment. The latter process, however, was not normal, since the ova that had been subjected to this treatment became transformed into masses of minute granules, and, instead of acquiring cilia and giving rise to embryonic individuals, they underwent a process of disintegration.

To Loeb belongs the credit of having done more than any other worker to elucidate the physico-chemical aspects of the phenomena of fertilisation. Loeb was the first definitely to succeed in producing plutei from the unfertilised eggs of the sea-urchin. His original method was to expose the eggs for about two hours to sea-water in which the degree of concentration had been raised by about forty or fifty per cent. This effect could be produced by the addition of sodium chloride, but it was found to be immaterial what particular substance was employed to raise the concentration, so long as it was one which did not act injuriously on the eggs. The ova were afterwards restored to normal sea-water, when they began to undergo segmentation and subsequently developed into normal plutei.

Loeb was able to show, further, that the parthenogenetic development of the ova in such cases was brought about by a loss of water. Thus, when the concentration of the sea-water was less than forty per cent., some of the ova of the sea-urchin *Arbacia* could be induced to develop, even though they were allowed to remain in the hypertonic solution. By adopting similar methods a like result could be effected for the other species of sea-urchin, and also in the case of the starfish *Asterias forbesii*; but it was necessary, as a general rule, to restore the ova to normal sea-water, as the continuance of abnormal conditions, although it might not hinder segmentation, usually arrested the further course of development.[2]

It was found, however, that osmotic fertilisation differed in several respects from fertilisation by a spermatozoön. Firstly, the ova fertilised by the former method began to segment without developing a membrane such as is invariably formed in normal eggs shortly after the entrance of the spermatozoa. Secondly, the rate of development in the artificially fertilised eggs was considerably slower than in the eggs fertilised by spermatozoa. Thirdly, the larvæ arising from osmotic parthenogenesis, as soon as they began to swim, did so at the bottom of the dish in which they were placed, instead of rising to the surface of the water like normal larvæ. It was found also that the percentage of eggs which could be induced to develop by the osmotic process was invariably very much smaller than the percentage of normally fertilised eggs which underwent development. The consideration of these differences led Loeb to conclude that the spermatozoön in normal fertilisation carried into the ovum not one, but several substances or conditions, each of which was responsible for a part only of the normal characteristics of the process; and that, in order to imitate successfully the action of the sperm, it would be necessary to combine two or more artificial methods.

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[1] Morgan, "The Action of Salt Solutions on the Unfertilised and Fertilised Ova of *Arbacia*, etc.," *Arch. f. Entwick.-Mech.*, vol. iii., 1896, and vol. viii., 1899.

[2] Loeb (J.), "On the Nature of the Process of Fertilisation, etc." *Amer. Jour. of Physiol.*, vol. iii., 1899. "On the Artificial Production of Normal Larvæ from the Unfertilised Eggs of the Sea-Urchin (*Arbacia*)," *Amer. Jour. of Physiol.*, vol. iii., 1900. "On Artificial Parthenogenesis in Sea-Urchins," *Science*, vol. xi., 1900. "Further Experiments on Artificial Parthenogenesis, etc.," *Amer. Jour. of Physiol.*, vol. iv., 1900. These papers are reprinted in Loeb's *Studies in General Physiology*, vol. ii., Chicago, 1905.

When the eggs of *Strongylocentrotus purpuratus* were put into 50 cubic centimetres of sea-water to which 3 c.c. of a decinormal solution of a fatty acid had been added, and were left in this water for about a minute, and were then transferred to ordinary sea-water, they were observed to form membranes. It was also noticed that the eggs underwent internal changes characteristic of nuclear division, but they were rarely seen to segment. Subsequently they began to disintegrate, and after twenty-four hours were nearly all dead. If, however, the ova, after they had formed a membrane, were deposited in sea-water which had been rendered hypertonic by adding 15 c.c. of sodium chloride solution of two and a half times the normal concentration, to 100 c.c. of sea-water, all or nearly all the eggs could be induced to develop. Furthermore, the rate of development was practically the same as that of normally fertilised eggs, a large percentage of the blastulæ looked normal and rose to the surface of the water, and the plutei which developed showed the usual degree of vitality.

The brothers Hertwig[1] had previously discovered that sea-water saturated with chloroform induced the unfertilised eggs of the sea-urchin to develop membranes. Herbst[2] more recently showed that benzol, toluol, creosote, or oil of cloves produced a similar effect. Loeb[3] found that amylene and various other hydrocarbons and acids also called forth membrane formation, and that eggs which were subjected to these methods could be made to segment by subsequent treatment with hypertonic sea-water in the way described. The substances which called forth membrane formation can be divided into two groups, the first consisting of hydrocarbons and certain substitute products, and the second being comprised of certain acids. Loeb states also that the order in which the two agencies are employed is of vital consequence, for if the eggs are subjected to the membrane-forming solution after being placed in the hypertonic sea-water instead of before, they develop a membrane, but shortly afterwards disintegrate. As a result of this series of experiments he concludes that the process of membrane formation is an essential and not a secondary phenomenon.[1] He makes the further suggestion that membrane formation is brought about by a kind of secretory process, due to the squeezing out under pressure of a liquid substance from the interior of the ovum[2] (*cf.* Jenkinson, p. 182, above). According to this view the excretion of the fluid is the essential feature, while the actual formation of the membrane is probably only a secondary mechanical effect of the sudden secretion.

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[1] Hertwig (O. and R.), *Untersuchungen zur Morphologie und Physiologie der Zelle*, Jena, 1887.

[2] Herbst, "Über die künstliche Hervorragung von Dottermembranen, etc.," *Biol. Centralbl.*, vol. xiii., 1893.

[3] Loeb, *The Dynamics of Living Matter*, New York, 1906. This work contains further references. "On an Improved Method of Parthenogenesis," Univ. of California Publications: *Physiology*, vol. ii., Berkeley, 1904.

In the case of the starfish it was found that the process of artificial membrane formation was alone sufficient to induce parthenogenetic development without any further treatment with hypertonic sea-water. This observation is connected by Loeb with the fact that starfish eggs are sometimes able to develop in the absence of any external cause or agency. Parthenogenetic development of starfish eggs has been produced also by mechanical agitation;[3] but it is possible, as Loeb observes, that the diffusion of carbonic dioxide, or some other gas, into or from the eggs may be the real exciting cause.[4]

Loeb found also that the unfertilised eggs of the Annelid *Chætopterus* could be made to develop into swimming larvæ by adding a small quantity of a soluble potassium salt to the sea-water in which they were placed.[5] The same result could be brought about by the addition of hydrochloric acid. The eggs appeared to undergo development, as far as the trochophore stage, but without segmenting.

Lillie[6] (F.), however, found that the nuclear divisions were abnormal, and that the apparent trochophore larvæ were not typical, being in reality merely "ciliated structures" which were far behind the real

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[1] It was found, however, that in the case of the starfish a very small number of eggs could develop without first forming a membrane, and that this number could be increased by transitorily treating the eggs with acidulated sea-water. See below.

[2] Loeb, "Ueber die Natur der Lösungen, etc.," *Pflüger's Arch.*, vol. ciii., 1904.

[3] Mathews, "Artificial Parthenogenesis produced by Mechanical Agitation," *Amer. Jour. of Physiol.*, vol. vi., 1901.

[4] Loeb, *The Dynamics of Living Matter*, New York, 1906.

[5] Loeb, "Experiments on Artificial Parthenogenesis in Annelids, etc.," *Amer. Jour. of Physiol.*, vol. iv., 1901.

[6] Lillie, "Differentiation without Cleavage in the Egg of the Annelid *Chætopterus pergamentaceus*," *Arch. f. Entwick.-Mechanik*, vol. xiv., 1902.

larvæ in organisation. But Bullot[1] showed that in another Annelid, *Ophelia*, ova fertilised by hypertonic sea-water underwent a regular segmentation.

Loeb has shown that the ova of limpets (*Acmæa* and *Lottia*) could be artificially fertilised by the combined action of fatty acid and hypertonic sea-water. This method also had the effect of hastening maturation, since ova which could not be fertilised by spermatozoa could be made to develop into larvæ by the artificial treatment. It was found, further, that maturation could be induced by the action of alkaline sea-water, and that ova which were treated in this way could be fertilised by spermatozoa or artificially fertilised.[2]

Bataillon[3] states that the unfertilised eggs of the lamprey, and also those of the frog, can be made to undergo segmentation as far as the morula stage by depositing them in a salt solution of such a concentration that they lose water. Sugar solutions were also found to be effective.[4] The unfertilised eggs of the frog can be made to segment also, and in many cases to develop into tadpoles and even to undergo metamorphosis by puncturing them with a needle.[5]

Various experiments have been tried with the object of finding out whether ova could be fertilised by substances artificially extracted from spermatozoa, but so far without any positive result.[6] Thus Gies attempted to obtain an enzyme from spermatozoa, with a view to seeing if such a substance would exert any influence on the unfertilised ovum, but his experiments lent no support to the idea.[7] Pizon's[8] experiments on the same question were also negative in result. (See p. 317.)

Loeb[9] has discussed at some length the question as to whether any idea can be formed regarding the nature of the action of the spermatozoön in causing the ovum to develop. He stated his belief that the essential effect of the spermatozoön consists in the transformation of part of the protoplasmic or reserve material in the egg into the specific nuclein or chromatin substance of the nucleus. In

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[1] Bullot, "Artificial Parthenogenesis and Regular Segmentation in an Annelid (*Ophelia*)," *Arch. f. Entwick.-Mechanik*, vol. xviii., 1904.

[2] Loeb, Univ. of California Publications: *Physiology*, Berkeley, vol. i., 1903, and vol. iii., 1905.

[3] Bataillon, "Nouveaux Essais de Parthénogénèse expérimentale chez les Vertébrés inférieurs (*Rana fusca* et *Petromyzon planeri*)", *Arch. f. Entwick.-Mechanik*, vol. xviii., 1904.

[4] Loeb, *loc. cit.*

[5] For an account of the experiments and further references see Loeb, *Artificial Parthenogenesis and Fertilisation*, Chicago, 1913.

[6] See Loeb, *The Dynamics of Living Matter*, New York, 1906.

[7] Gies, "Do Spermatozoa contain Enzyme having the Power of causing Development of Mature Ova?" *Amer. Jour. of Physiol.*, vol. vi., 1901.

[8] Pizon, "Recherches sur une prétendue Ovulase des Spermatozoïdes," *C. R. de l'Acad. des Sciences*, vol. cxli., 1905.

[9] Loeb, *loc. cit.*

each nuclear division one-half of the mass of each original chromosome goes into the nucleus of each of the two resulting cells. But during the resting period which elapses until these nuclei are ready to divide again, each chromosome grows to its original size, and then a new division occurs. It is quite possible that the oxygen which is required for the process of cell division is needed for the synthesis of nuclein or chromatin substance. The fact that the rate of development is influenced by temperature, in much the same way as are chemical reactions, supports the idea given above that the essential feature of fertilisation consists in the starting or the acceleration of a chemical reaction which is going on steadily in the egg. Loeb was disposed to conclude, therefore, that the spermatozoön acts as a positive catalyser, but further evidence has led him to reject this idea as improbable. He pointed out that, if it were correct, normal sea-urchin eggs should segment if kept for a sufficiently long period, and that it ought to be possible to induce segmentation by applying heat, since heat is known to accelerate chemical reactions, but neither of these results could be obtained.

He then suggested the possibility that the spermatozoön, in conjugating with the ovum, removed from the latter a negative catalyser or condition whose existence in the ovum somehow inhibits the process of development. This suggestion seemed to provide an explanation of the secretory phenomena, which, on Loeb's hypothesis, are the cause of the membrane formation. "Finally, we may be able to understand a fact which [has been] observed in the eggs of a starfish, and which has not yet been mentioned, when the eggs of *Asterina* or *Asterias* are allowed to ripen, they will die within a few hours unless they develop either spontaneously or through the influence of sperms or some of the above-mentioned agencies. The disintegration which leads to the death of the non-developing egg is obviously due to an oxidation, since I found that the same eggs when kept in the absence of oxygen will not disintegrate. We know that oxygen is an absolute prerequisite for the development of the fertilised egg" [but this statement is disputed by Delage]. The fact that oxygen is a poison for the mature but non-developing egg shows that the chemical processes which occur in the unfertilised, non-developing egg must be altogether different from those which go on in the developing egg of the starfish.[1]

[1] Loeb, *loc. cit.* See also "The Toxicity of Atmospheric Oxygen for the Eggs of the Sea-Urchin after the Process of Membrane Formation"; "On the Necessity of the Presence of Free Oxygen in the Hypertonic Sea-water for the Production of Artificial Parthenogenesis"; "On the Counteraction of the Toxic Effect of Hypertonic Solutions upon the Fertilised and Unfertilised Egg of the Sea-Urchin by lack of Oxygen," Univ. of California Publications: *Physiology*, vol. iii., 1906. See also "Versuche über den Chemischen Charakter des Befruchtungsvorgangs," *Biochem. Zeitsch.*, vol. i., 1906. "Weitere Beobacht-

Loeb's conclusion was that the phenomenon of fertilisation (as studied in the sea-urchin, the starfish, *Lottia*, *Polynœ*, and Sipunculids) consisted essentially, firstly, in a liquefaction or hydrolysis (or both) of certain fatty compounds in the ovum, and secondly, in an initiation in the right direction of a new process of oxidation.[1] These changes which occur in the fertilised egg lead to the synthesis of nuclein material from the protoplasm. According to this view, the process of astrosphere formation is not the direct effect of the act of fertilisation, but is a secondary consequence of the new chemical changes which are brought about by the entrance of the spermatozoön.

In a later work Loeb[2] has elaborated his theory further. Membrane formation is regarded as an essential factor in normal fertilisation, and is of the nature of a cytolysis of the egg, for all cytolytic agents (*e.g.* foreign blood or cell extracts) produce it. Normally the fertilisation membrane is brought about by a lysin carried in by the sperm, which also carries another substance that serves to counteract the evil effects of membrane formation (p. 194).

Delage,[3] however, has adduced experimental evidence, some of

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ungen über den Einfluss der Befruchtung und der Zahl der Zellkerne auf die Säurebildung im Ei," *Biochem. Zeitsch.*, vol. ii., 1906; "Über die Superposition von künstlichen Parthenogenese und Samenbefruchtung in demselben Ei," *Arch. f. Entwick.-Mechanik*, vol. xxiii., 1907; "Über die allgemeinen Methoden der künstlichen Parthenogenese," *Pflüger's Arch.*, vol. cxviii., 1907; and other papers in the same volume. The following papers also deal with artificial parthenogenesis in various animals: Delage, *C. R. de l'Acad. des Sciences*, vol. cxxxv., 1902 (describing fertilisation by anæsthetisation with carbon dioxide during maturation); and *C. R. de l'Acad. des Sciences*, vol. cxli., 1906 (describing fertilisation with various salt solutions); Treadwell, "Notes on the Nature of Artificial Parthenogenesis in the Egg of *Patella obscura*," *Biol. Bull.*, vol. iii., 1902; Scott, "Morphology of the Parthenogenetic Development of *Amphitrite*," *Jour. of Exper. Zool.*, vol. iii., 1906; Lefevre, "Artificial Parthenogenesis in *Thalassema mellita*," *Jour. of Exper. Zool.*, vol. iv., 1907; Kostanecki, "Zur Morphologie der künstlichen parthenogenetischen Entwicklung bei *Mactra*," *Arch. f. Mikr. Anat.*, vol. lxxii., 1908. See also Mathews, whose paper has been already referred to (Chapter IV., p. 129, "A Contribution to the Chemistry of Cell Division, Maturation, and Fertilisation," *Amer. Jour. of Physiol.*, vol. xviii., 1907). This author lays stress on the part played by the centriole, and suggests "that the various methods employed to produce artificial parthenogenesis do not do so by their direct physical action on the cell, but indirectly by producing in one way or another active centriole substance in the cell cytoplasm, or by causing its discharge from the nucleus."

[1] Loeb, "The Chemical Character of the Process of Fertilisation and its bearing upon the Theory of Life Phenomena."—Address before the International Congress of Zoologists, Boston, 1907, Univ. of California Publications, vol. iii., 1907.

[2] Loeb, *Die chemische Entwicklungserregung des tierischen Eies*, Berlin, 1909; *Artificial Parthenogenesis and Fertilisation*, Chicago, 1913; and Lillie, *Problems of Fertilisation*, Chicago, 1919. These important works contain full references. For further discussion of the subject see p. 313 See also pp. 185 and 194.

[3] Delage, "Les Vrais Facteurs de la Parthénogénèse Expérimentale," *Arch. de Zool. Expér. et Gén.*, vol. vii., 1908.

which is opposed to Loeb's interpretation of the observed phenomena. This investigator has shown that it is possible artificially to fertilise sea-urchins' eggs by treating them with solutions of tannin and ammonia. He had already formed the conception that the essential facts of cell division could be resolved into a succession of processes involving coagulation and liquefaction. The formation of the vitelline membrane is said to be essentially a coagulative process (and also possibly the formation of the centrosome and of the nuclear spindle), and the dissolution of the nuclear membrane and certain of the accompanying events are regarded as evidence of liquefaction. These considerations led Delage to employ tannin as an agent for inducing coagulation, and ammonia for causing liquefaction. Tannate of ammonia was found to produce a similar effect, but this is explained by Delage on the assumption that, since tannin is a feeble acid and ammonia is a feeble base, the ammonium tannate becomes dissociated, so that the acid function (which brings about coagulation) and the alkaline function (which causes liquefaction) may be supposed to coexist in the solution, and so separately to exert an influence on different parts of the egg. By adopting the above-described method, Delage succeeded in artificially fertilising ova, so that they developed into complete sea-urchins, but it is curious to note that the symmetry of these individuals was liable to be abnormal, one of them being hexameral instead of pentameral. Delage also obtained successful results by using carbon dioxide and other agents, and starfishes' eggs as well as sea-urchins' were successfully fertilised. Furthermore, certain of the experiments seemed to indicate that the presence of oxygen is not an important factor (as supposed by Loeb), since development could be induced after the oxygen present had been very largely eliminated (but see pp. 186-197).

It is, of course, obvious that Loeb's interpretation of the observed phenomena of fertilisation among the Metazoa is inapplicable to the process of gametic union in the Protozoa, in which the conjugating units are often apparently similar and equipotential, and the same objection may be offered to Delage's theory. It is possible, however, that conjugation in the Protozoa, while presenting an essential similarity to fertilisation in the Metazoa, initiates a series of chemical processes of a relatively simpler kind. Moreover, the theory that the changes consequent upon gametic union are the result of a catalytic chemical reaction is in no way opposed to the vaguer physiological conception that the object of the process is to secure a rejuvenescence of vital substance without which the race cannot be perpetuated.

The cytological changes which occur in artificially fertilised ova have been dealt with at considerable length by Wilson, to whose paper[1] the reader is referred. It is shown that the ovum of the sea-urchin, under an appropriate stimulus, is able to construct the complete mechanism of mitotic cell division without the importation of a sperm-centrosome, but beyond this a multitude of aberrations are exhibited. The number of chromosomes is one-half that occurring in normally fertilised eggs, being in the sea-urchin eighteen instead of thirty-six. The centrosomes are primarily formed *de novo.* According to Delage,[2] however, the number of chromosomes in artificially fertilised sea-urchins becomes eventually restored to the normal by a process of auto-regulation.

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[1] Wilson (E. B.), "Experimental Studies in Cytology: I. A Cytological Study of Artificial Parthenogenesis in Sea-Urchin Eggs," *Arch. f. Entwick.-Mechanik*, vol. xii., 1901. For an account of the cytological phenomena in normal parthenogenetic eggs, especially in insects, see Hewitt, "Cytological Aspects of Parthenogenesis in Insects," *Memoirs and Proc. Manchester Literary and Philosophical Soc.*, vol. l., 1906.

[2] Delage, "Études expérimentales sur la Maturation Cytoplasmique chez les Échinodermes," *Arch. de Zool. Expér. et Gén.*, vol. ix., 1901. *Cf.* also Tennent and Hogue, "Studies on the Development of the Starfish Egg," *Jour. of Exp. Zool.*, vol. iii., 1906.

CHAPTER VII

THE ACCESSORY REPRODUCTIVE ORGANS OF THE MALE AND THE MECHANISMS CONCERNED IN INSEMINATION

> "Mais, par ce moyen de propagation seminale, demeure es enfans ce qu'estoit de perdu es parens et es nepveux ce que dépérissoit es enfans, et ainsi successivement."—Rabelais.

A brief description of the mammalian testis has already been given in a chapter on the physiology of the spermatozoön (p. 159). It remains, however, to state what is known regarding the functional relations of the accessory male organs, and to refer incidentally to the homologous structures in the female.

After traversing the tubules of the rete testis the spermatozoa, swimming in the seminal fluid, make their way into the vasa efferentia, which open into the canal of the epididymis. The vasa efferentia in man are about twenty in number. Before passing into the epididymis they become convoluted, forming the coni vasculosi. Both the vasa efferentia and the tube of the epididymis contain smooth muscular fibres in their walls. They are lined internally by columnar epithelial cells provided with long cilia which assist the muscles in expelling the semen.

Passing away from the epididymis, and in continuation with its canal, is the vas deferens, which is nearly two feet long in the human subject, and has an average diameter of about one-tenth of an inch. It possesses a plain muscular wall, consisting of an outer layer of longitudinal, a middle of circular, and an inner of longitudinal muscles. On the inside of the muscles there is a mucous coat lined by a columnar epithelium, which is not ciliated.[1]

A branch from one of the vesical arteries accompanies the vas deferens, and eventually enters the testis, where it anastomoses with the spermatic artery. The vas deferens, near its termination, becomes sacculated, and in this region is known as the ampulla of Henle. In the walls of the ampulla there are a number of small tubular glands, which doubtless supply some portion of the ejected fluid.

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[1] The epithelium of the vas in some animals (rat) is apparently ciliated. Arising from the lower part of the epididymis, or from the vas deferens close to its commencement, is a long narrow diverticulum which ends blindly. This is the vas aberrans. It is probably a vestigial structure. A few small convoluted tubes, situated near the head of the epididymis and representing vestiges of part of the Wolffian body, are called the paradidymis or organ of Giraldès. The innervation of the vas deferens is described below (p. 269).

Disselhorst[1] believes that the ampulla acts as a seminal reservoir (a function which has also been assigned to the vesiculæ seminales, as described below), and states that he has found spermatozoa stored up in little pockets in the walls of this structure in animals during the rutting time. He suggests, further, that there is a relation between the state of development of the ampulla and the time occupied by copulation. When the organ is small or absent, as in dogs, cats, and boars, the coition is a slow process, but when the ampulla is large and well-developed, as in horses and sheep, the coitus occupies a relatively short time.

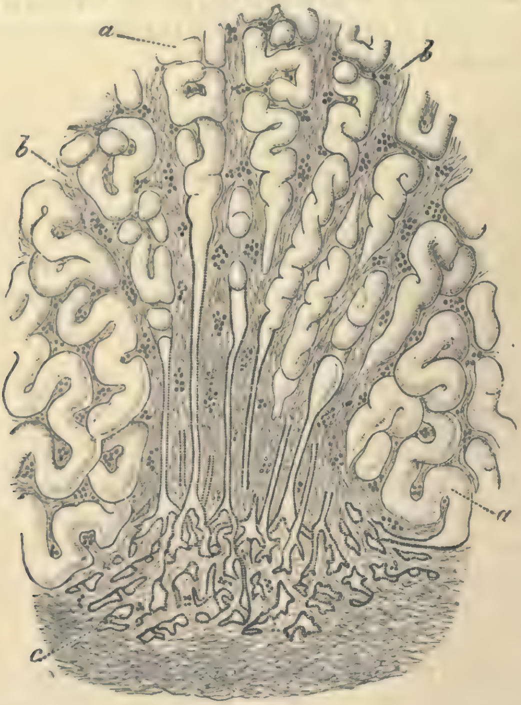

Fig. 62.—Passage of convoluted seminiferous tubules (*a*) into straight tubules, and of these into rete testis (*c*) (after Mihalkowicz, from Schafer); *b*, fibrous stroma continued from mediastinum.

The vas deferens on either side unites with the terminating portion of the corresponding seminal vesicle to form the ejaculatory duct. The two ejaculatory ducts, after traversing the prostate, open into the floor of the urethra by small slit-like apertures. Their function is to convey to the urethra the fluid contained in the seminal vesicles and in the vasa deferentia. The coats of the ejaculatory ducts are relatively thin. The lining epithelium is similar to that of the vas deferens.

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[1] Disselhorst, "Ausführapparat und Anhangsdrüsen der Männlichen Geschlechtsorgane," Oppel's *Lehrbuch der Vergleichenden Mikroscopischen Anatomie der Wirbeltiere*, vol. iv., Jena, 1904.

The urethra, which serves as the common channel for both urine and seminal fluid, is lined by a columnar epithelium resting on a vascular corium. The latter is surrounded by submucous tissue containing two layers of muscular fibres, the inner being arranged longitudinally, and the outer circularly. The urethra in man is usually described as consisting of three divisions, the prostatic, the membranous, and the spongy portions. Of these the membranous portion comprises that part of the urethra between the apex of the prostate and the bulb of the corpus spongiosum, to be described below. Opening medially into the prostatic portion of the urethra, between the two ejaculatory ducts, is the aperture of the uterus masculinus, or organ of Weber, which is the homologue of the vagina and uterus in the female. This vesicle, which is a small *cul-de-sac*,

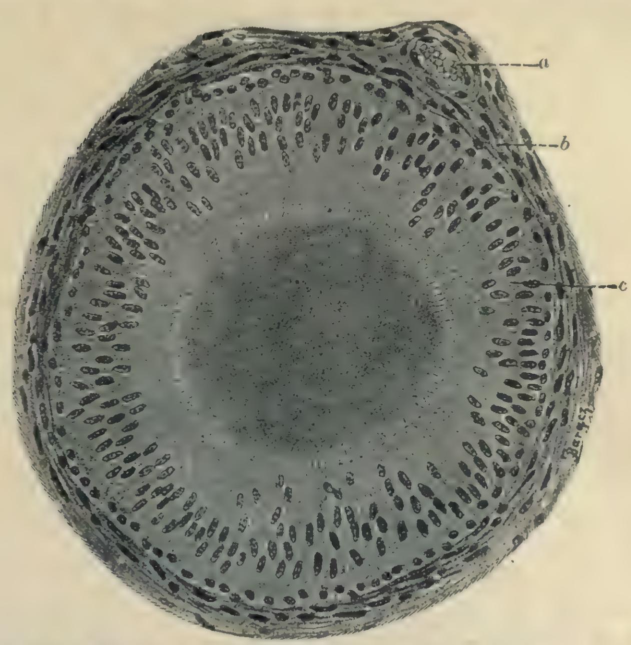

FIG. 63.—Transverse section through the tube of the epididymis. (After Szymonowicz, from Schafer.)

a, Blood-vessel ; *b*, circular muscle fibres ; *c*, epithelium.

and in man lies hidden by the prostate, is probably almost or quite functionless, but it has a few very small glands which open into its cavity. In some animals—such as the goat, for example—it is of comparatively large dimensions, the upper part being divided into two horns. In connection with it is a structure corresponding to the hymen of the female. On the floor of the prostatic portion of the urethra is an elevation of the mucous membrane and underlying tissue, known as the crista urethra or caput gallinaginis. This eminence (which contains erectile tissue) serves when distended with blood to prevent the semen from passing backwards to the bladder, and mingling with the urine in the process of emission. It is assisted in this function by the contraction of the sphincter of the bladder.

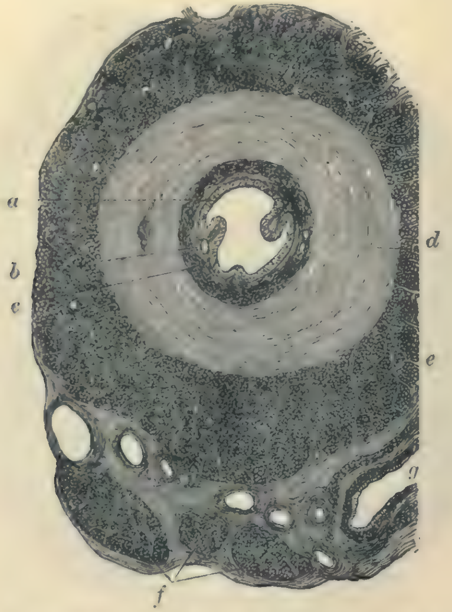

Fig. 64.—Transverse section through commencement of vas deferens. (After Klein, from Schafer.)

a, Epithelium ; *b*, mucous membrane ; *c*, *d*, *e*, inner, middle, and outer layers of muscular coat ; *f*, internal cremaster muscle ; *g*, blood-vessel.

The urethra in the female corresponds to that part of the male urethra which is anterior to the openings of the ejaculatory ducts. It is lined with a stratified scaly epithelium, like that of the vagina.[1] Communicating with the female urethra are two complex tubular glands known as the glands of Skene. Their ducts open very close to the urethral aperture.

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[1] See footnote on p. 71 for interrelationships of female organs.

The Vesiculæ Seminales

The seminal vesicles are offshoots from the lower ends of the vasa deferentia. They consist in man of coiled tubes, about five inches long, into which several diverticula sometimes open. The structure of the vesicles is similar to that of the sacculated part of the vas deferens, but the muscular layers are relatively thinner.

There has been some dispute as to the chief function of the seminal vesicles. According to one view, they serve mainly as receptacles for the spermatozoa before ejaculation. Most authorities, however, are disposed to lay greatest stress upon their secretory function.

Rehfisch[1] has shown that if fluids are injected into the testicular end of the vas deferens, they first enter the seminal vesicle and afterwards pass out through the urethra. He concludes that the vesiculæ serve the double purpose of secretory glands and reservoirs for the semen.[2] Misuraca[3] states that in dogs and cats, which have no seminal vesicles,[4] the spermatozoa disappear from the male passages from five to seven days after castration, whereas in guinea-pigs, in which the vesicles are well developed, sperms may be found alive as long as twenty days after the removal of the testes. This is regarded as evidence that the seminal vesicles function as receptacles for the spermatozoa. Moreover, Meckel[5] stated that he found sperms in the vesiculæ of the mole in the month of February (*i.e.* during the breeding season); and Seubert[6] recorded a similar observation about the hedgehog in August (also in the breeding season) (*cf.* p. 55). Disselhorst,[7] however, throws some doubt on these observations. The present writer[8] has examined the contents of the vesiculæ of the hedgehog at all seasons of the year and has failed to find spermatozoa even after the most careful search and during the middle of the breeding season.

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[1] Rehfisch, "Neuere Untersuchungen über die Physiologie der Samenblasen," *Deutsche med. Wochenschr.*, vol. xxii., 1896.

[2] It has been pointed out that the passage of spermatozoa into the vesiculæ probably only occurs during the asphyxia of death in consequence of the constriction of the vas deferens which forces the contained fluid into these organs (Luciani, *Human Physiology*, English Edition, vol. v., London, 1921).

[3] Misuraca, "Sopra un importante questione relativa alla castrazione," *Rivista sperimentale di Freniatria*, vol. xv., 1890.

[4] Seminal vesicles are absent not only in dogs and cats, but in many other Carnivora, and also in Cetacea and Ruminantia. They are also wanting in rabbits, but are present in the vast majority of Rodentia (Owen, *Comparative Anatomy*, vol. iii., London, 1868).

[5] Meckel, *Beiträge zur Vergleichende Anatomie: 1. Ueber die Männlichen eschlechtsteile des Maulwurfs*, 1809.

[6] Seubert, "Symbolum ad Erinacei europæi anatomen," *Inaug. Dissert.*, Bonn, 1841.

[7] Disselhorst, *loc. cit.*

[8] Marshall, "The Male Generative Cycle in the Hedgehog," *Jour. of Physiol.*, vol. xliii., 1911.

That the vesiculæ may undergo periodic enlargement in animals which have a rutting season is an unquestionable fact. In the hedgehog the increase in size is enormous. In the winter they are hidden by the bladder and their weight may be only ·1 gram. In August the weight of the organs, together with their contained secretion, was found to be 6 grams, and they occupied a considerable space in the body cavity. In April they were about one-fifth their full size. In May they had reached their full size which they retained until September or October, when they rapidly diminished.

As evidence that the vesiculæ seminales are undoubtedly secretory glands, Lode[1] showed that in young animals, in which one of the testes had been removed, the corresponding vesicula continued to grow, and became filled with its characteristic fluid. It was evident, therefore, that the fluid must have been secreted in the vesicula in question, since it could not have been derived from the testis of the other side. (The effects of complete castration on the growth and activity of the vesiculæ seminales are briefly referred to below.) Stilling[2] and Akutsu[3] state that the epithelial cells of the vesiculæ seminales change their character according to whether they are in a state of rest or activity. In the former condition they are larger and contain more plasma substance. Kolster[4] has described desquamation of epithelial cells in the seminal vesicles of the elk (*Cervus alces*).

The secretion is formed apparently in considerable quantity. Its character and composition vary somewhat in different Mammals. In man it is gelatinous, and consists chiefly of globulins.[5] It has been investigated in Rodents by Sobotta,[6] Rauther,[7] and others,[8] who describe it as a white or yellowish-white gelatinous fluid, which becomes almost solid after ejaculation. This capacity to clot is supposed by Landwehr[1] to be due to the presence of fibrinogen, twenty-seven per cent. of which was found to be present. Calcium, however, could not be discovered. Camus and Gley[2] state the clotting is brought about by a specific ferment (which they call vesiculase) in the prostatic secretion (see p. 248).

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[1] Lode, "Experimentelle Beiträge zur Physiologie der Samenblasen," *Sitzungsber. d. kais. Acad. d. Wissenschaft in Wien*, vol. civ., 1895.

[2] Stilling, "Beobachtungen über die Functionen der Prostata und über die Entstehungen prostatischer Concremente," *Virchow's Archiv*, vol. xcviii., 1884.

[3] Akutsu, "Mikroscopische Untersuchung der Secretionsvorgänge in den Samenblasen," *Pflüger's Archiv*, vol. xcvi., 1903. Further references are given in this paper.

[4] Kolster, "Ueber einen eigenartigen Prozess in den Samenblasen von *Cervus alces*," *Arch. f. Mikr. Anat.*, vol. lx., 1902.

[5] Fürbringer, "Die Störungen des Geschlechtsfunktion des Menschen," Nothnagel's *Pathologie und Therapie*, vol. xix., 1895.

[6] Sobotta, "Die Befruchtung und Furchung des Eies der Maus," *Arch. f. Mikr. Anat.*, vol. xlv., 1895.

[7] Rauther, "Ueber den Genitalapparat einiger Nager und Insektivoren, etc.," *Jenaische Zeitsch. f. Naturwissenschaft*, vol. xxxvii., 1903.

[8] De Bonis, "Sui Fenomenidi Secrezione nelle Cellule ghiandolari delle Vescicule Seminale e delle Ghiandole di Cowper," *Arch. Ital. di Anat. e di Embryol.*, vol. vii., 1908. Abstract in *Arch. Ital. de Biol.*, vol. lii., 1909.

The clotting of the fluid, after its entrance into the female passages in Rodents, prevents the escape of the spermatozoa and so helps to ensure fertilisation. This fact was first discovered by Lataste,[3] who speaks of the "bouchon vaginal" formed by the solidified secretion of the vesiculæ. Similar observations have been made by Leuckart[4] and others. The "bouchon vaginal" is said to remain *in situ* for several hours, and then to become softened and fall out.

The vesiculæ of the hedgehog during the breeding season contain a great quantity of yellowish-white fluid containing a large number of irregularly shaped crystals resembling small ill-formed crystals of edestin. Hopkins[5] has examined chemically the centrifugal precipitate obtained from the vesicular fluid, and found it to consist mainly of a peculiar phospho-protein which differed from most other phospho-proteins in its resistance to solution in alkalis. He regards its existence in such large quantity in a physiological secretion as a remarkable and exceptional phenomenon which must presumably have some peculiar significance. It has not been described as present in the vesicular fluid of other Mammals.

Tarchanoff[6] has suggested that in the frog the filling of the seminal vesicles serves to excite sexual feeling in the male during the breeding season. He states that the injection of milk, by causing distension, excited sexual desire. But certain other observations have been made which seem to disprove Tarchanoff's conclusions (or at any rate to show that they are not universally true). Thus, in some animals, it is known that sexual desire exists before the seminal vesicles become full. Moreover, Steinach[7] found that rats, whose seminal vesicles had been removed, still retained their desire for copulation although their fertility was diminished.[1]

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[1] Landwehr, "Ueber den Eiweisskörper (fibrinogene Substanz) der Vesicula seminalis der Meerschweinchen," *Pflüger's Archiv*, vol. xxiii., 1880.

[2] Camus and Gley, "Note sur quelques faits relatifs à l'énzyme prostatique (vésiculase) et sur la fonction des glandes vésiculaires," *C. R. de Soc. de Biol.*, vol. iv. (10th series), 1897.

[3] Lataste, "Sur le bouchon vaginal des Rongeurs," *Zool. Anz.*, vol. vi., 1883.

[4] Leuckart, *Zur Morphologie und Anatomie der Geschlechtsorgane*, Göttingen, 1847.

[5] Hopkins, Addendum to Marshall's paper, *loc. cit.*

[6] Tarchanoff, "Zur Physiologie des Geschlechtsapparates des Frosches," *Pflüger's Archiv*, vol. xl., 1887.

[7] Steinach, "Untersuchungen zur Vergleichenden Physiologie der Männlichen Geschlechtsorgane, etc.," *Pflüger's Archiv*, vol. lvi., 1894.

That the spermatozoa possess complete functional activity before they can be in any way influenced by the secretion of seminal vesicles has been conclusively shown by Iwanoff,[2] who induced pregnancy artificially in rabbits, guinea-pigs, and other animals, by injecting into the female passages fluid obtained directly from the epididymis, and mixed with a five per cent. solution of sodium carbonate. The diminished fertility in Steinach's rats, after the removal of the vesiculæ, was probably due to the absence of formation of the "bouchon vaginal," as has been suggested by Rauther.

It would seem probable that, in the majority of animals which possess vesiculæ seminales, the secretion of these glands serves to dilute the semen, and so assists in providing a fluid medium for the transference of the spermatozoa.

Exner[3] has suggested that the seminal vesicles may have the function of absorbing the seminal fluid which is not ejaculated, but there is little evidence that this is the case.

Lode[4] found that in castrated bulls, horses, and guinea-pigs the glandular epithelium of the vesicles atrophied, but the connective tissue underwent hyperplasia. Gruber[5] and Pelikann[6] observed that in castrated men the glands atrophied, but became filled with a kind of mucous liquid.

Steinach[7] has shown that in rats early castration inhibits the development of the vesiculæ. Further, castration in the hedgehog done in winter prevents the seasonal growth of these glands in the following spring. Unilateral castration, however, has no effect, the vesiculæ developing with normal symmetry.[8] Vasectomy has also no effect.

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[1] If both vesiculæ and prostate were removed complete sterility resulted (see below). See also Nussbaum, "Ueber den Bau und die Tätigkeit der Drüsen," *Arch. f. Mikr. Anat.*, vol. lxxx., 1912.

[2] Iwanoff, "La Fonction des Vésicles seminales et la Glande prostatique," *Jour. de Phys. et de Path. Gén.*, vol. ii., 1900. See also papers in *C. R. de la Soc. de Biol.*, vols. lxxiv. to lxxx., 1913-17.

[3] Exner, "Physiologie der Männlichen Geschlechtsfunktionen," Frisch and Zuckenhandl, *Handbuch der Urologie*, 1903.

[4] Lode, *loc. cit.*

[5] Gruber, "Untersuchung einiger Organe eines Castraten," *Müllers Archiv.*, 1847.

[6] Pelikann, *Gerichtl.-mediz. Unters. über d. Skopzentum in Russland*, Giessen, 1876.

[7] Steinach, "Untersuchung zur vergleichenden Physiologie der männlichen Geschlechtsorgane," *Pflüger's Arch.*, vol. lvi., 1894. See also *Zent. f. Phys.*, vol. xxiv., 1910.

[8] Marshall, *loc. cit.*

THE PROSTATE GLAND

The prostate in man and other Mammals is a tubular gland which surrounds the urethra at the base of the bladder, and opens into it by a number of small ducts situated close to the apertures of the ejaculatory ducts. It is usually described as consisting of three lobes, two lateral and one median, the former comprising the chief mass of the organ. Associated with the glandular substance is a considerable quantity of plain muscular tissue. The prostate is provided with lymph-vessels and blood-vessels. The arteries arise from the vesical, hæmorrhoidal, and pudic arteries. The veins communicate with the dorsal vein of the penis and with the internal iliac vein.[1] The innervation of the gland is described below in dealing with the mechanism of ejaculation (p. 268).

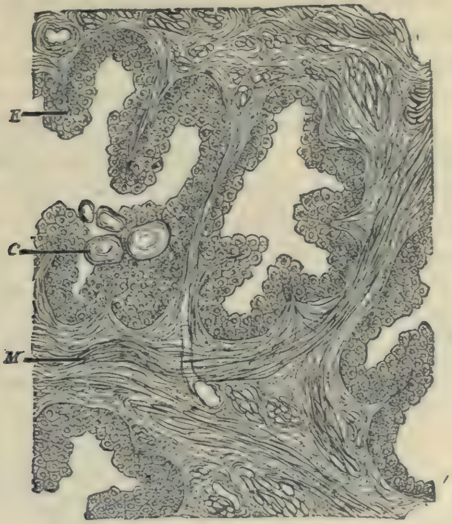

FIG. 65.—Section through part of human prostate. (After Heitzmann, from Schafer.)

C, Concretions, often found in old subjects ; *E*, epithelium ; *M*, muscular tissue.

The prostatic secretion is a viscid, slightly acid liquid (sometimes neutral or even alkaline), containing proteins and salts[2] (see p. 301). The characteristic smell of the ejected seminal fluid is said to be partly due to the prostate secretion, which also contributes to the formation of Böttcher's crystals described below (p. 299).

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[1] See Richardson, *The Development and Anatomy of the Prostate Gland*, London, 1904.

[2] Poehl, *Die Physiol.-chem. Grundlage der Spermintheorie*, St. Petersburg, 1898 ; Fürbringer, *Die Störungen der Geschlechtsfunktion des Mannes*, Wien, 1895 ; *Berliner klin. Wochenschrift*, vol. xxiii., 1886.

De Bonis[1] describes the epithelial cells of the dog's prostate as containing a small number of granules. When these have been formed in sufficient quantity, so as almost to fill the cell, its wall ruptures and the granules pass out into the lumen of the gland. This occurs especially during coitus. After the discharge of the granules fresh ones are formed in the cells of the gland.

Little is definitely known regarding the function of the prostate beyond the fact that it contributes additional fluid to the semen. It also appears to cleanse the urethra of urine prior to the ejaculation of semen, since in a stallion (for example) the first fluid to be expelled in sexual intercourse appears to be prostatic fluid and contains no spermatozoa. It may, perhaps, assist in providing the spermatozoa with nutriment.[2] There is some evidence, however, that it exercises a stimulating influence upon the movements of the spermatozoa.[3] Steinach observed that prostatic fluid, when added to normal saline solution, kept the spermatozoa in active movement for a longer period than saline solution alone. Steinach also found that rats in which the prostate gland, together with the seminal vesicles, was extirpated, were absolutely sterile,[4] but this may have been due to failure to form a "bouchon vaginal" in the female. As already mentioned (p. 245), the clotting which causes the formation of the "bouchon" in Rodents is believed by Camus and Gley[5] to be due to a ferment ("vesiculase") which is present in the prostatic fluid.[6] The removal of the prostate in Steinach's experiments had no effect in diminishing sexual desire.

Walker[7] has also adduced experimental evidence pointing to the conclusion that the prostatic fluid of the dog stimulates the sperms to more active movement.

Iwanoff[8] also states that the secretion causes the spermatozoa to become active, but at the same time to shorten their life. Earlier experiments by Iwanoff (see p. 246), however, show that spermatozoa which have never come into contact with prostatic secretion possess full functional activity, and are capable of fertilising ova successfully.[1]

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[1] De Bonis, "Über die Sekretionserscheinungen in den Drüsenzellen der Prostata," *Arch. f. Anat. u. Phys.*, Anat. Abth., 1907.

[2] It has been suggested also that the prostate is a sphincter of the bladder, but this is rendered unlikely by its absence in the female.

[3] Fürbringer, *loc. cit.* Kölliker, "Physiologische Studien über die Samenflüssigkeit," *Zeitsch. f. wiss. Zool.*, vol. vii., 1856.

[4] Extirpation of the vesiculæ seminales alone produced only partial sterility (see p. 246). Walker (*Johns Hopkins Hospital Reports*, 1911) obtained similar results.

[5] Camus and Gley, *loc. cit.*

[6] According to Walker the secretion which causes the clotting is produced by a special gland which he calls the "coagulating gland" (*Johns Hopkins Hospital Bull.*, vol. xxi., 1910). See below, p. 300.

[7] Walker (G.), "Beitrag zur Kenntniss der Anatomie und Physiologie der Prostata beim Hunde," *Arch. f. Anat. u. Phys.*, Anat. Abth., 1899.

[8] Iwanoff, "Ueber die physiologischen Rolle der accessorischen Geschlechtsdrüsen, etc.," *Arch. f. Mikr. Anat.*, vol. lxxvii., 1911. See also Vichnersky (*Roussk Vratchi*, vol. viii., 1909; abstract in *Jour. de la Phys. et la Path. Gen.*), who found that prostatic secretion obtained by merely squeezing the gland had no effect on sperm movement, but that got by stimulation of nerves caused energetic movement. The properties lasted three days in the cold, but were less marked after boiling. See also Iwanoff, etc., *C. R. Soc. Biol.*, vol. lxxx.

Serralach and Parès[2] have adduced evidence indicating that the prostate is an internally secreting gland which controls the testicular functions, and regulates the process of ejaculation. It is stated that if the prostate is removed spermatozoa are no longer produced in the testis, and that the secretory activity of the accessory genital glands ceases. These changes, however, can be prevented by the administration of glycerine extracts of prostate gland. The experiments were upon dogs. The most obvious criticism of Serralach and Parès' view is that it is unlikely, on phylogenetic grounds, that the functional

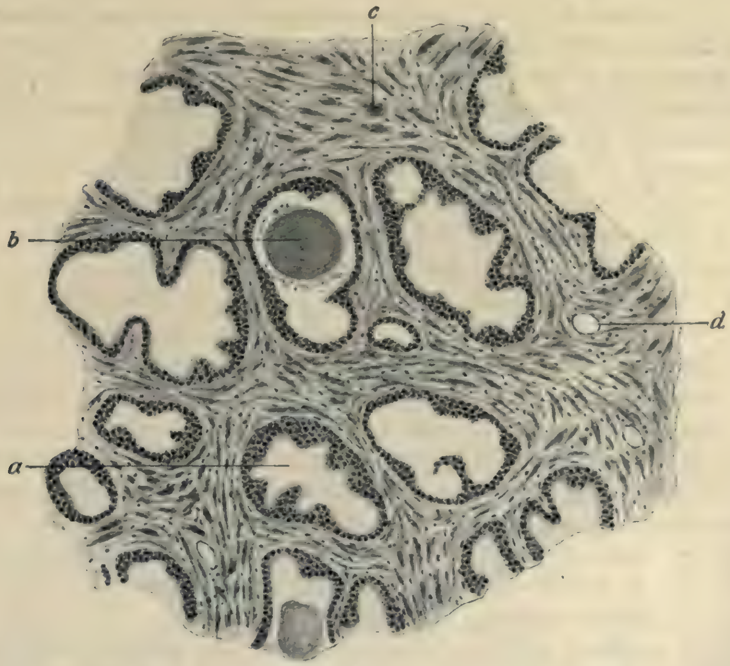

Fig. 66.—Section through prostate gland of monkey.

a, Tubular alveolus lined with epithelium ; *b*, alveolus containing concretion in lumen ; *c*, bundle of muscular fibres in connective tissue ; *d*, blood-vessels in stroma.

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[1] According to Herokawa (*Biochem. Zeitsch.*, vol. xix., 1909) the influence of prostatic fluid on spermatozoa is due to its alkalinity. The addition of small quantities of alkali to physiological salt solution was found to be favourable to spermatozoa.

[2] Serralach and Parès, "Quelques données sur la Physiologie de la Prostate et du Testicule," *C. R. de la Soc. Biol.*, vol. lxiii., 1908.

activity of the essential organ of reproduction should depend on the presence of an accessory gland of comparatively recent evolutionary development. On the other hand, it is arguable that the prostate may originally have formed part of the testis, and subsequently have become differentiated as a separate organ in the course of phylogeny. Reference may be made in this connection to the somewhat similar theory, which certain gynæcologists have held, that the ovarian functions are dependent on an internal secretion arising in the uterus, whereas the most recent experimental evidence proves clearly that this is not the case (see p. 376).

According to Lichtenstein[1] extirpation of the prostate has no influence on the development of the secondary male characters or on sexual desire (*cf.* Steinach, above).[2]

Griffiths[3] has shown that the prostate glands in the hedgehog and the mole undergo definite cyclical changes which are correlated with changes in the functional activity of the testes (*cf.* p. 243). In the quiescent state the prostate is composed of a few tubules lined by small, flattened, epithelial cells, which are at this time incapable of producing a secretion. With the approach of the breeding season the tubules grow much larger and the epithelial cells become columnar. During rut the prostate gland is a mass of tortuous tubules, and has grown to eight to ten times the size of the quiescent organ.[4] The tubules are described as being filled with coagulated mucus, containing a number of small round cells resembling leucocytes; while the epithelial cells are said to show numerous mucigenous granules, especially in the inner or lumen half, but also, though less markedly, in the outer half of each cell (*cf.* de Bonis' description of the dog's prostate referred to above).[5]

The prostatic secretion is expelled into the urethra during the sexual act by the contraction of the sheath of non-striped muscle which surrounds each tubule throughout its entire length.

It has been shown in both man and animals that the growth of the prostate is dependent upon the growth of the testes, since it remains of small size until the time of puberty, when the generative system reaches its full development. In those abnormal cases in which testicular growth is arrested, the prostate remains in a condition of rudimentary development. Moreover, it has been shown that the prostate in man normally undergoes atrophy in old age (see p. 718), or as a result of castration, becoming transformed after a few years into a mass of fibrous connective tissue containing a small number of scattered muscle fibres in a state of degeneration. It has been found also that the prostatic tubules disappear almost entirely in castrated animals, and what is left of the epithelium completely loses its secretory function[1] (*cf.* p. 320). De Bonis' experiments, however, seem to show that the administration of prostatic extract to castrated dogs may lead to a renewal of activity and to the formation of fresh granules in the secretory cells, but this result could not be obtained by employing testicular extract.

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[1] Lichtenstein, "Untersuchungen über die Funktion der Prostate," *Zeitsch. f. Urologie*, vol. x., 1916.

[2] But *cf.* Ott and Scott, p. 272 below, footnote at end of chapter.

[3] Griffiths, "Observations on the Function of the Prostate Gland in Man and the Lower Animals," *Jour. of Anat. and Phys.*, vol. xxiv., 1890.

[4] Marshall, *loc. cit.*

[5] See also Griffiths, "Observations on the Anatomy of the Prostate," *Jour. of Anat. and Phys.*, vol. xxiii., 1889. For the comparative anatomy of the prostate, see Oudemans' *Die Accessorischen Geschlechtsdrüsen der Säugethiere*, Haarlem, 1892. According to this authority, the hedgehog has two pairs of prostates. The homologies of these glands in Insectivores still seem to be obscure. See below, under Cowper's glands.

Castration in the hedgehog, done in winter, stops the periodic enlargement of the prostate (just as with the vesiculæ), while the partial operation has no effect.[2] Vasectomy also has no effect.

COWPER'S GLANDS

Cowper's glands are situated near the anterior end of the urethra. They are a pair of small tubulo-racemose glands, and communicate with the urethra by two ducts, apertures of which (in the human subject) are about two inches below the openings of the vasa deferentia. The lobules of the glands are surrounded by a firm investing membrane which contains muscular tissue. They are lined internally by a secretory epithelium.

The significance of the viscous secretion which these glands produce is still unknown. It has been suggested that it serves to cleanse the urethra of urine or semen; also that it produces an alkaline secretion which neutralises the acidity caused by the urine. Since it is poured out in considerable quantity during coitus, and appears sometimes to precede the ejaculation of the actual semen, it is not impossible that the secretion of these glands may possess the special function of ridding the urethra of all traces of urine preparatory to the passage of the spermatozoa. The glands of Littré or Morgagni, which beset the whole lining membrane of the urethra, except near the external orifice, probably serve the same purpose as Cowper's glands. (*Cf.* prostate, p. 248.)

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[1] Griffiths, *loc. cit.* *Cf.* also Griffiths, "The Condition of the Testes and Prostate Gland in Eunuchoid Persons," *Jour. of Anat. and Phys.*, vol. xxviii., 1893; Walker (G.), "Experimental Injection of Testicular Fluid to prevent the Atrophy of the Prostate Gland after the Removal of the Testes," *Johns Hopkins Hospital Bull.*, vol. xi., 1900; Wallace (Cuthbert), "Prostatic Enlargement," London, 1907; de Bonis, *loc. cit.*

[2] Marshall, *loc. cit.*

According to Nagel,[1] Cowper's glands are of the normal dimensions in castrated men, and consequently should not be regarded as purely sexual organs. According to Barrington,[2] removal of the glands in rats and guinea-pigs has no effect on their breeding powers.[3] On the other hand, Schneidemühl,[4] whom Nagel quotes, says that in animals they atrophy after castration. Griffiths[5] describes these glands in the hedgehog and the mole as undergoing periodic changes similar to those of the prostate glands. In the hedgehog the secretion is abundant during the summer (*i.e.* in the breeding season), and possesses a disagreeable and penetrating odour. According to Gley,[6] the secretion in this animal contains a ferment which causes the fluid of the vesiculæ seminales to clot, so that Cowper's glands in the hedgehog may be the physiological equivalent of the prostate gland in the Rodentia.[7] Furthermore, Stilling[8] states that the epithelium of Cowper's glands undergoes definite histological changes which depend upon the occurrence of coitus.[9]

Corresponding to Cowper's glands in the male there are in the female a pair of small glands situated one on each side of the vagina.

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[1] Nagel, "Physiologie der Männlichen Geschlechtsorgane," *Nagel's Handbuch der Physiologie des Menschen*, vol. ii., Braunschweig, 1906.

[2] Barrington, "The Variations in the Mucin Content of the Bulbo-Urethral Glands," *Int. Monatsschr. für Anat. und Phys.*, vol. xxx., 1913.

[3] Double ovariotomy in adults reduces the size of the glands and inhibits the secretion of mucin (Barrington).

[4] Schneidemühl, "Vergleichende Anatomische Untersuchungen über den feineren Bau der Cowperschen Drüse," *Deutsche Zeitsch. f. Tiermedizin*, vol. vi., 1883.

[5] Griffiths, "Observations on the Function of the Prostate Gland, etc.," *Jour. of Anat. and Phys.*, vol. xxiv., 1890.

[6] Gley, "Rôle des Glandes génitales accessoires dans la Reproduction," *Nel primo Centenario dalla Morte di Lazzaro Spallanzani Acad. Sci. e Stranieri*, 1899.

[7] It should be mentioned that very considerable doubt has been thrown on the homology of what are often called Cowper's glands (those presumably referred to by Gley and Griffiths) in the hedgehog with the glands known by that name in other Mammals. According to Leydig ("Zur Anatomie der Männlichen Geschlechtsorgane und Analdrüsen der Säugethiere," *Zeitsch. f. wiss. Zool.*, vol. ii., 1850), Cowper's glands in the hedgehog are in reality represented by a pair of glands embedded in the urethral muscle (*cf.* Oudemans, *loc. cit.*). The so-called Cowper's glands, which, as mentioned above, undergo marked cyclical changes, are situated outside the pelvis close to the ischial tuberosity and the base of the penis (Linton, "A Contribution to the Histology of the so-called Cowper's Glands of the Hedgehog," *Anat. Anz.*, vol. xxxi., 1907). In the absence of embryological evidence, Linton appears to regard these glands as *sui generis.* They are shown by this author to be composed of two distinct kinds of secreting acini, one lined by a single layer of columnar epithelial cells, and the other by many layers of polyhedral cells. Both kinds secrete a considerable quantity of fluid, containing circular bodies which are believed to be the nuclei of disintegrated cells, though no cells in process of disintegration could be found in the single-layered type of acinus.

[8] Stilling, "Über die Cowperschen Drüsen," *Virchow's Arch.*, vol. c., 1885.

[9] For an exhaustive account of the minute anatomy of the accessory glands and ducts of the male reproductive system in the different groups of Vertebrata, with full references to the literature, see Disselhorst in *Oppel's Lehrbuch*, *loc. cit.*

These are the glands of Bartholini or Duverney. Their ducts open out on to the vulva (between the hymen—posterior segment—and labia minora). These glands secrete a viscid fluid which helps to moisten and lubricate the surface of the vulva.

Barrington has shown that the secretory fibres to the glands in the cat are contained in both the hypogastric and pelvic visceral nerves, the former controlling the secretion of mucin. He believes Cowper's glands to be innervated in the same way.

In addition to the accessory male glands described above, there are, in many animals, other glands (perineal, inguinal, and preputial) which are probably sexual, inasmuch as they are believed to serve as means of attraction between the sexes during the breeding season.[1] Most of these glands emit secretions of a musky odour, which in the vast majority of cases is peculiar to the male, and very often to the male during the rutting season only. Amongst the animals in which this peculiarity occurs are the musk deer and other kinds of deer and antelopes, the musk rat, the hamster, and many other Rodentia and Insectivora. The temporal gland of the elephant is also stated to emit a sexual secretion, especially in the male during rut.

The Copulatory Organ

The penis is the intromittent organ of copulation. Besides serving to conduct the urine to the exterior through the channel of the urethra, it has the further function of conveying the semen into the genital passages of the female. This latter function is dependent upon its power of erection under the influence of sexual excitement.

The erectile tissue of the penis is contained chiefly in three tracts, the two corpora cavernosa, which are situated one on each side and are united in the middle line, and the smaller corpus spongiosum, which is placed inferiorly and surrounds the urethral passage. The corpora cavernosa are enclosed by an investment, containing plain muscle fibres, numerous well-developed elastic fibres, as well as bundles of white fibres. Trabeculæ pass inwards from the fibrous sheath and cross the cavities of the cavernous bodies, dividing them into interstices which are filled with venous blood, being, in fact, greatly enlarged vessels. The corpus spongiosum is similar in structure, but its fibrous framework is not so well developed. The canal of the urethra is surrounded by plain muscle fibres. Muscular tissue is also present in the external coat of the spongy body, and in the trabeculæ.

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[1] Tiedemann, *Comparative Physiology*, English Translation, London, 1834; Gross, "Beiträge zur Anatomie der Geschlechtsdrüsen der Insektivoren und Nager," *Arch. f. Mikr. Anat.*, vol. lxvi., 1905. See also description of prepuce (p. 254).

At their proximal ends the three corpora are enlarged into bulbs. Those of the cavernous bodies are covered by the ischio-cavernosi muscles (or erectores penis), while the bulb of the spongy body is surrounded by the bulbo-cavernosus muscle (or ejaculator urinæ). At its distal end the corpus spongiosum becomes enlarged, forming the glans penis, which is identical in structure with the rest of the body.

The integument of the penis in the region of the glans becomes doubled in a loose fold. This is the prepuce or foreskin. Numerous sebaceous glands are present near the free margin of the prepuce. These glands emit an odoriferous secretion which in some animals is especially marked during the season of rut.[1]

The penis is very sensitive to external stimulation, its surface being beset with simple and compound end-bulbs and Pacinian corpuscles, especially in the region of the glans.

The various kinds of end-organs in the external genital organs of both sexes have been described at some length by Luciani,[2] to whose work the reader is referred. There are genital corpuscles, the nerve fibres to which divide into five branches which end in knobs (Krause's end-bulbs), as well as typical Meissner's corpuscles which are capsulated and usually oval or elongated in shape, with a complex and variable structure, and a series of transitional forms passing imperceptibly from Pacinian corpuscles to more elaborate structures. The end-organs in the glans penis are not uniformly distributed, and Head,[3] taking advantage of this fact, was able to carry out an interesting experiment illustrating sensory dissociation and the inhibition of afferent impulses by other antagonistic impulses which become dominant. It was found that the tip of the glans may be devoid of heat-spots or end-organs responding to the sensation of heat, but in possession of others which are sensitive to cold and pain. In such a case "the end of the penis was dipped into a glass containing water at 40° C.; since no heat-spots were present and this temperature has no effect upon the cold-spots, the only sensation evoked was a peculiarly disagreeable pain. When, however, the temperature of the water was raised to 45° C., pain was to a great extent displaced by a vivid sensation of cold, due to stimulation of the cold-spots. Instead of increasing the discomfort an elevation of temperature ceased to be strictly painful because of the appearance of the specific sensation of 'paradox cold.' But around the corona the penis is always well furnished with heat-spots in addition to those for cold and for pain; as soon then as the water at 45° C. covered the corona without reaching the foreskin, both cold and pain disappeared, giving place to an exquisitely pleasant sensation of heat." "In none of these cases was the process of selective inhibition in any way conscious. The sensation evoked was a definite one of heat, of cold, or of pain, but it was the final issue of a struggle between incompatible and mutually antagonistic afferent impulses."

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[1] Courant, "Über die Präputialdrüsen des Kaninchens und über Veränderungen derselben in der Brunstzeit," *Arch. f. Mikr. Anat.*, vol. lxii., 1903.

[2] Luciani, *Human Physiology*, English Translation, edited by Holmes, vol. iv., London, 1917.

[3] Head, "Release of Function in the Nervous System," Croonian Lecture, *Proc. Roy. Soc.*, B., vol. xcii., 1921. See also Head, with Rivers, Holmes, Sherren, Thompson, and Riddoch, *Studies in Neurology*, London, 1920.

The arteries of the penis are the internal pudic arteries and the

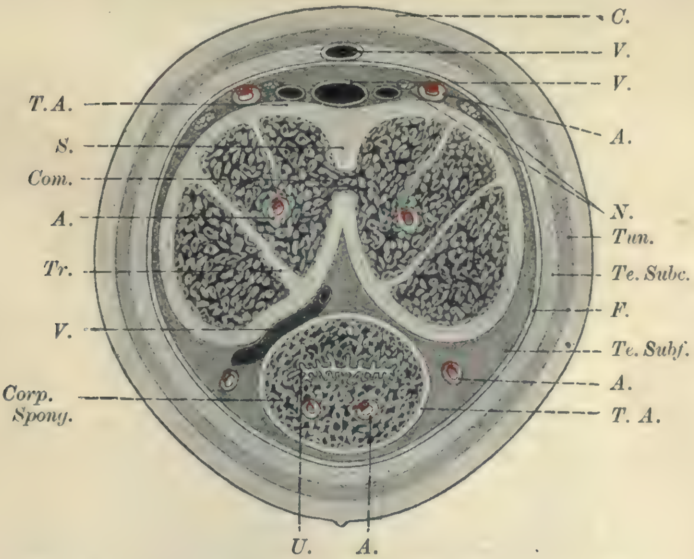

Fig. 67.—Transverse section through adult human penis. ×3. (After Eberth, from Nagel.)

A., Artery; *C.*, cutis; *Com.*, communication between the two corpora cavernosa; *Corp. Spong.*, corpus spongiosum; *F.*, fascia; *N.*, nerves; *S.*, septum; *T. A.*, tunica albuginea; *Te. Subc.*, tela subcutanea penis; *Te. Subf.*, tela subfascialis; *Tun.*, tunica dartos penis; *Tr.*, trabeculæ of corpus cavernosum; *U.*, urethra; *V.*, veins.

dorsal artery. Some of the arterial branches project into the intertrabecular spaces of the corpora cavernosa, and form coiled dilated vessels which are known as the helicine arteries. In these arteries the intima is folded, thus rendering them capable of great dilatation. Moreover, these arteries present here and there a thickening of the intima in the form of little cushions which constitute a valvular apparatus which limits the flow of blood into the corpora cavernosa, when the muscular coat assumes the tonus that exists when the penis is flaccid.[1] In most cases the arteries are said to open into the venous spaces, through the intervention of capillaries, but a few of the smaller arteries are stated to communicate directly with the cavernous veins. The blood is carried away by two sets of veins, the one set uniting to form the dorsal vein, and the other communicating with the prostatic plexus and the pudendal veins.

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[1] Luciani, *loc. cit.*

When the venous spaces in the erectile tissue are distended with blood the organ erects, becoming hard and rigid in condition. It is this power of erection which enables the penis to function as an intromittent organ during copulation.

The above description applies more especially to the copulatory organ in man. In the other groups of Mammals it has essentially the same structure, but presents sundry modifications in the different orders.[1] In the Monotremata, however, there is no corpus spongiosum.[2] In some Mammals (Carnivora and Rodentia) the penis is provided with a cartilaginous or bony support, the os penis, which is developed especially in the region of the glans. It is

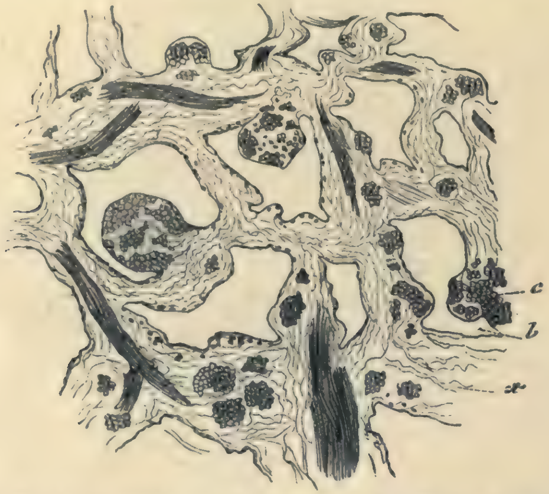

Fig. 68.—Section through erectile tissue. (After Cadiat, from Schafer.)
a, Trabeculæ ; *b*, venous spaces ; *e*, muscular fibres cut across.

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[1] For an account of the structure of the copulatory organ in the various groups of Vertebrates, with notes on the different modes of copulation and bibliography, see Gerhardt, "Morphologische und biologische Studien über die Kopulationsorgane der Säugethiere," *Jenaische Zeitsch. f. Naturwissenschaft*, vol. xxxix., 1905.

[2] The penis of the Monotreme is perforated by a canal, through which the semen passes but not the urine. When in a relaxed state the organ lies in a little pouch in the floor of the cloaca, from which it projects when erected. The cloaca is the single common chamber through which the fæces and urine pass to the exterior, as in birds and reptiles. In birds the penis is either altogether absent or else is rudimentary (*Crax*, *Crypturus*, Lamellirostres, Ratitæ), Disselhorst, "Gewichts- und Volumszunahme der männlichen Keimdrüsen, etc.," *Zool. Anz.*, vol. xxxii., 1908.

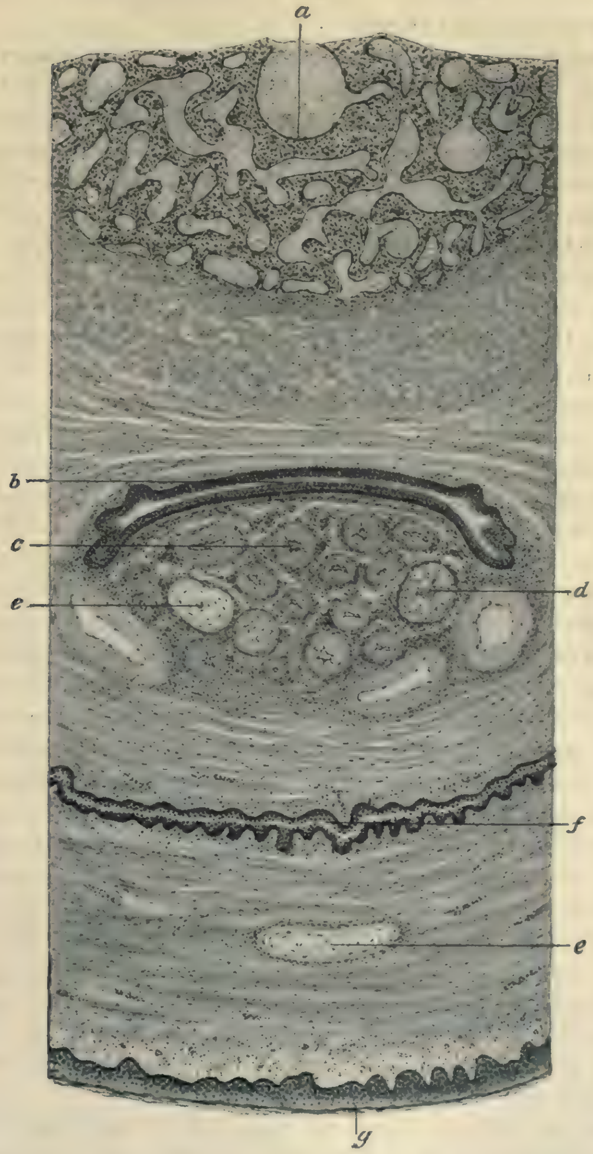

FIG. 69.—Part of transverse section through penis of monkey.

a, Erectile tissue ; *b*, urethra ; *c*, artery ; *d*, nerve ; *e*, Pacinian body ; *f*, fold of epithelium ; *g*, surface epithelium.

particularly large in the walrus. In the Cetacea the penis is often of enormous size (six feet in length in some species), and terminates in a point, but is otherwise normal. It can be withdrawn into the body when not being used. In copulation, whales apply their ventral surfaces to one another.

In most Rodents and Marsupials the penis in the relaxed state is withdrawn within an eversible fold of skin which constitutes a dermal sac. When the penis is erected this sac is everted, and forms its outer integument. Cole has described the structure of the intromittent sac in the male guinea-pig, which appears to be typical of many other Rodents.[1] Dorsal to the urethral aperture when the penis is withdrawn, and ventral to it when it is everted, is seen the entrance to the intromittent sac. Lying in the cavity of the sac are two horny styles. Two dorsal longitudinal folds are also noticeable. These are the backward prolongations of the lateral lips of the urethral aperture, the ventral lip consisting of corpus spongiosum and separating the aperture of the urethra from that of the sac. Attached to the base of the sac are two retractor organs which consist of elastic fibres and erectile tissue, and are connected at their other extremities with the integument of the penis. The eversion of the sac is brought about by the erection of the two longitudinal folds referred to above. The whole of the sac is composed largely of erectile tissue, but the tissue of the longitudinal folds is even more highly erectile than the rest of the sac. The entire structure is provided with a very rich nerve supply. When the penis is erect, and the sac everted, the two horny styles are protruded externally to a considerable length. Moreover, both the sac and the surface of the glans are covered with sharp spine-like structures, while in some species of Caviidæ they are provided also with two sharp horny saws which are appended to the sides of the penis farther back. There can be little doubt that the purpose of this unique contrivance is to act as an exciting organ on the sexual structures of the female.

In another rodent, the marmot, according to Gilbert[2] the skin which covers the os penis becomes torn away during the rutting season, so that the bone projects freely beyond the end of the glans and is then used as a stimulating organ.

Structures which project from the penis, and are probably employed as sexual irritants, are also found in the rhinoceros, the tapir, and certain other animals.

In the cat the glans is beset with callous retroverted papillæ, which no doubt serve the same function. They are present also in the lion and tiger, but are of smaller size.[3]

Perhaps the most curious modifications presented by the mammalian organ of copulation are those found in certain species of

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[1] Cole, "On the Structure and Morphology of the Intromittent Sac of the Male Guinea-Pig," *Jour. of Anat. and Phys.*, vol. xxxii., 1898.

[2] Gilbert, "Das Os priapi der Säugethiere," *Morph. Jahrbuch*, vol. xviii.

[3] Owen, *On the Anatomy of Vertebrates*, vol. iii., London, 1868.

Ruminants. In the sheep, the gazelle, the giraffe, and a number of antelopes, there is a long filiform process attached to the end of the organ and traversed by the urethral passage. In some forms the process arises medially (the penis being symmetrical); but in others, such as the sheep, it is attached to the left side of the organ, the distal end of which appears to have undergone some sort of torsion.[1]

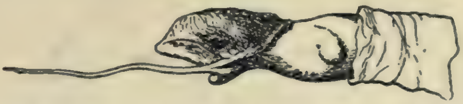

FIG. 70.—Distal end of ram's penis, as seen from the left side, showing glans and filiform appendage. The prepuce is folded back. Slightly reduced.

The urethra opens to the exterior at the extreme end of the filiform appendage. This structure—which has been investigated, especially in the case of the sheep[2]—is composed largely of erectile tissue which surrounds the urethra, and may be regarded as an extension of the corpus spongiosum. Outside the erectile tissue is a well-marked muscular layer which lies next to the integument. The process is supported by a pair of fibro-cartilage bodies, placed one on each side of the urethra and extending throughout the whole length of the structure.

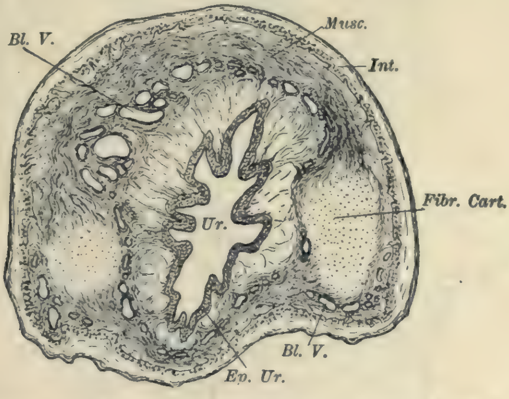

FIG. 71.—Transverse section through filiform appendage of ram, about a quarter its length from the tip. ×45.

Bl. V., Blood-vessels ; *Ep. Ur.*, epithelium surrounding urethral cavity ; *Fibr. Cart.*, fibro-cartilage ; *Int.*, integument ; *Musc.*, muscular layer ; *Ur.*, urethra.

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[1] Garrod, "Notes on the Osteology and Visceral Anatomy of Ruminants," *Proc. Zool. Soc.*, vol. xlv., 1877. For other orders see below, pp. 261 and 272.

[2] Nicolas, "Sur l'Appareil Copulateur du Bélier," *Jour. de l'Anat. et la Phys.*, vol. xxiii., 1887. Marshall, "The Copulatory Organ in the Sheep," *Anat. Anz.*, vol. xx., 1901.

The fact that the filiform prolongation is an erectile organ points to the conclusion that its function is insertion into the os uteri during copulation. An examination of the uterus in the sheep shows that the os, when open, is fully large enough to admit of the entrance of the distal portion of the penis in the region of the glans. If the extreme distal end does so enter, the filiform process must extend into the cavity as far, or nearly as far, as the junction of the relatively short corpus uteri with the two cornua. That the appendage functions in the manner described seems additionally probable in view of the fact, to which sheep-breeders attest, that if the process is

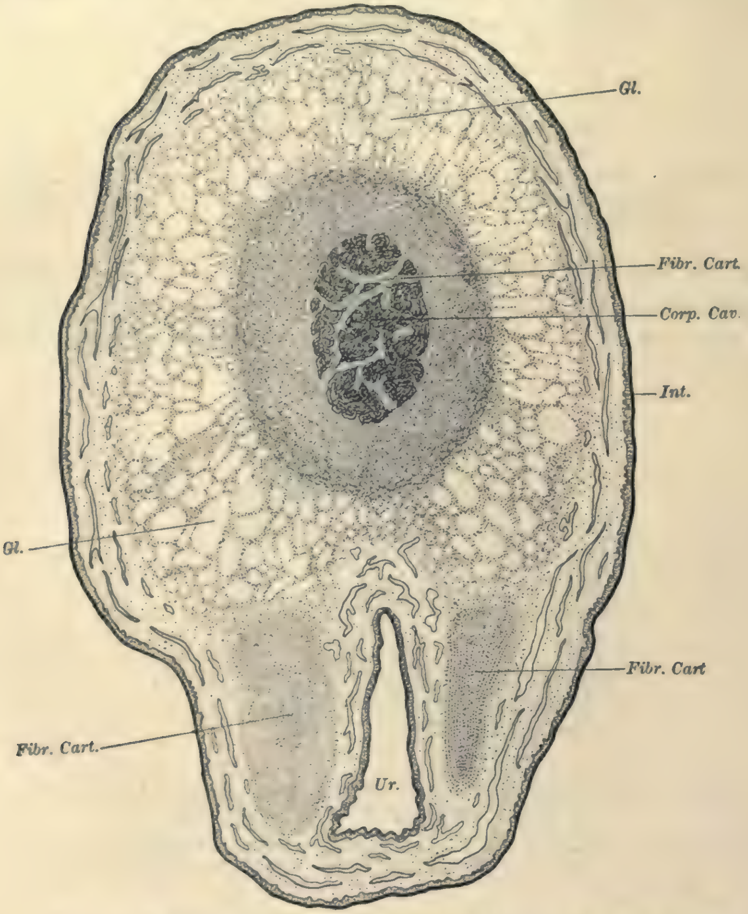

Fig. 72.—Transverse section through the middle of the glans penis of the ram. × 45.

Corp. Cav., Corpus cavernosum ; *Fibr. Cart.*, fibro-cartilage ; *Gl.*, erectile tissue of glans ; *Int.*, integument ; *Ur.*, urethra.

cut off the ram is rendered barren. Professor Robert Wallace informs me that it used to be a regular practice, for the protection of ewes while being driven south from the Highlands of Scotland, to cut off the filiform appendage from the rams to prevent them from impregnating the ewes on the way, this method of inducing sterility proving quite as effective as removal of the testicles.

In the bull, the musk ox, and some other Ruminants the filiform process is vestigial. The end of the penis itself (the glans) is somewhat pointed in the bulb and it is believed that it is inserted into the os uteri in copulation. It does not swell up to the same extent as in the stallion, where the erected organ almost fills the vagina of the mare and much friction takes place before ejaculation is completed. The urethral aperture is central in the horse, as in the boar.

In the dog the process of coition is very prolonged. This is due to the contraction of a sphincter in the female which prevents the withdrawal of the male organ until almost fully relaxed.[1]

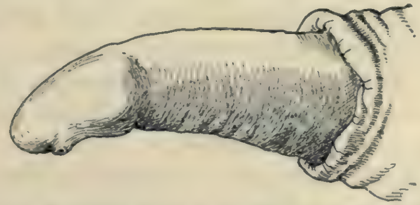

FIG. 73.—Distal end of bull's penis as seen from left side, showing glans and urethral papilla representing vestigial filiform appendage. The prepuce is folded back. About two-thirds natural size.

The penis in the male mammal is represented in the female by the diminutive clitoris. This organ, however, is not traversed by the urethra (at least in the majority of animals). On the other hand, the corpora cavernosa and the glans are represented by homologous structures. The clitoris, like the penis, contains very numerous sensory nerve endings[2] and undergoes erection during sexual congress.

The relation between the clitoris and the urogenital canal is closer in some Mammals than in others. In some species (*e.g.* the capybara among the Rodents, and *Tupaia* among Insectivores) the clitoris is of considerable size, and is grooved along its under surface in relation to the upper wall of the urethra. In other animals (*e.g.* *Arvicola*, *Talpa*, and *Stenops*) the groove on the under surface of the elongated clitoris is converted by the coalescence of its margins into a tube, which constitutes the urethral portion of the urogenital canal. Further, in the female of the spotted hyena (*H. crocuta*), the whole of the urogenital canal, beyond the apertures of the ducts of Bartholini's glands, is prolonged forward to the extremity of the clitoris and terminates in a similar manner to that of the urethra of the male. In this animal, therefore, the vagina is completely absent, the os uteri opening directly into the urogenital canal, which is elongated and tubular in form as in the male. A somewhat similar condition has been known to occur abnormally in the human female.[1]

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[1] Prolonged retention has also been known to occur with the human subject.

[2] Worthmann, "Beiträge zur Kenntniss der Nervenausbreitung in Clitoris und Vagina," *Arch. f. Mikr. Anat.*, vol. lxviii.

THE MECHANISMS OF ERECTION, EJACULATION, AND RETRACTION

The erection of the penis is brought about mainly by the dilatation of its blood-vessels. First of all the bulbous (proximal) part of the organ increases in size, and then the swelling extends throughout the cavernous bodies, and eventually to the glans. If the penis is cut across when in a state of relaxation only a small quantity of venous blood exudes from the wound; but if the same operation is performed during erection, the blood flow is enormously increased, while simultaneously becoming bright and arterial in colour.[2] François-Franck[3] observed a corresponding rise in the arterial and venous tension. He found also that the organ in the process of erection became very considerably swollen in size before the increase in the blood pressure had extended to the veins. Lovén[4] showed that the veins in the penis are traversed by five times as much blood during erection as they are in a state of repose. The same investigator found that, whereas the ordinary arterial pressure in the penis is about half that of the carotid, during erection it rose to three-fifths that of the carotid. The increase in the amount of blood in the organ is accompanied by a rise of temperature.[5]

There can be no doubt that the erection of the penis is brought about partly through the contraction of the ischio-cavernosus (or erector penis) and bulbo-cavernosus muscles, certain of the fibres of which pass over the efferent vessels, and so arrest the outward flow of blood.[6] The result of this contraction is, that whereas the blood can freely enter the dilated vascular spaces of the penis, its exit is retarded, while this leads to a further distension of the vessels, the venous outlets of which become still more compressed.

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[1] Watson (M.), "The Homology of the Sexual Organs, etc.," *Jour. of Anat. and Phys.*, vol. xiv., 1879. See also note on p. 272 for other orders.

[2] Eckhard, "Untersuchungen über d. Erektion d. Penis beim Hunde," *Beitr. zur Anat. und Phys.*, vol. iii., Giessen, 1863.

[3] François-Franck, "Recherches sur l'Innervation Vaso-motrice du Pénis," *Arch. de Phys.*, 1895.

[4] Lovén, *Berichte über die Verhandlungen der Königl. Sachs. Gesell. zu Leipzig*, vol. viii., 1866. Nikolsky, "Ein Beitrag zur Physiologie der Nervi erigentes," *Arch. f. Anat. u. Phys.*, Phys. Abth., 1879.

[5] Retterer, Article on "Erection," in Richet's *Dictionnaire de Physiologie*, vol. v., 1902.

[6] De Graaf (Regner), *De Virorum Organis Generationi Inservientibus*, Geneva, 1785. Günther, *Untersuchungen und Erfahrungen aus dem Gebiete der Anatomie*, vol. i., Hanover, 1837. Kobelt, *De l'Appareil du Sens Génital des Deux Sexes*, Strasbourg, 1851. For further references, see Retterer, *loc. cit.*

Although the muscular mechanism of the penis unquestionably assists in the erection of that organ, it is equally clear that it is incapable by itself of causing that phenomenon, since erection cannot be induced by ligaturing the efferent veins. Moreover, the penis can be made to erect in animals in which the muscular mechanism has been paralysed by the injection of curari, but the erection in such cases is incomplete.

It is stated also that the smooth or unstriated muscle fibres, which are scattered throughout the trabecular framework of the corpora, participate in the process of erection, but there has been some disagreement as to the precise part they play. Kölliker[1] suggested that their action is temporarily inhibited, and that the relaxation of the trabeculæ, which consequently follows, permits the vascular spaces to distend. According to Valentin,[2] these muscles contract, and in so doing cause a dilatation of the walls of the vessels, which thereby increase in volume. Langley and Anderson's observations, which support Kölliker's suggestion, are described below in giving an account of the nervous mechanisms of erection and retraction.

It is obvious, however, that in those cases in which the penis remains erected for a considerable time a constant circulation must be maintained through both the afferent and the efferent vessels of the organ.

In some animals (dog, cat, horse, hedgehog), but not in the rabbit or man, the penis possesses an accessory muscle. This is called the retractor penis. It consists of a thin band of longitudinally arranged, unstriated fibres, inserted at the attachment of the prepuce, and continued backwards in the middle line over the ventral surface of the corpus spongiosum to the bulbous part of the urethra, where it divides into two halves which separate on either side of the anus. Some of the fibres are continuous with a portion of the bulbo-cavernosus of the same side, while others are connected with the wall of the urethra. When it contracts it causes a marked dorsal curvature of the penis.[3]

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[1] Kölliker, *Verhandl. der Würzburger Phys. Med. Gesell.*, vol. ii., 1851.

[2] Valentin, *Lehrbuch der Physiologie*, vol. ii., 1844.

[3] Langley and Anderson, "The Innervation of the Pelvic and Adjoining Viscera: Part III. The External Generative Organs," *Jour. of Physiol.*, vol. xix., 1895. The retractor muscle is remarkable for its sensitiveness to changes of temperature, and at the same time for being unusually tenacious of life. It can be cut out of the body and preserved in blood-serum, in a cool place, for days at a time, and afterwards, on warming, will relax and undergo spontaneous contractions. At a temperature of 40° C. it is quite placid; but, on cooling

Although the sexual orgasm is usually accompanied by a high degree of mental excitement, it is essentially a reflex action, and can take place when all connection with the brain is severed by transection of the spinal cord. The friction which is set up between the male and female organs during coition causes a discharge of motor impulses in both sexes, the uterus undergoing a series of peristaltic contractions. Thus Heape[1] has described a sucking action on the part of that organ in the rabbit, the os uteri dipping down into the semen at the bottom of the vagina to be withdrawn again in co-ordination with a rhythmical contraction by the uterine muscles. At the same time the accessory sexual glands in the female (Bartholini's glands, etc.) discharge a secretion which is added to the semen.

It is generally believed that the centre for erection lies in the lumbo-sacral region of the cord.[2] Numerous experiments have been recorded which prove conclusively that it is not situated in the upper part of the cord or in the brain. Thus, Goltz[3] showed that transection of the spinal cord above the lumbar region did not destroy the reflex. Brachet[4] also has recorded the occurrence of ejaculation under a similar condition. According to Müller,[5] only the lower part of the cord need be retained in order to preserve the erection reflex, since this is still present after the complete destruction of the cord in the whole of the lumbar and the upper part of the sacral region. Müller was able to induce erection in a dog, which had undergone this operation, by rubbing the surface of the penis.[6]

It is known, however, that erection (and even ejaculation) can also be induced voluntarily by stimuli conveyed from the brain (*i.e.*

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slightly, it will shorten, and not infrequently enter into a series of slow rhythmic contractions. If cooled to 15° C. it will contract to about one-quarter of its original length. (Sertoli, "Contribution à la Physiologie Générale des Muscles lisses," *Arch. Ital. de Biol.*, vol. iii., 1883; Gruenhagen, "Das Thermotonometer," *Pflüger's Arch.*, vol. xxxiii., 1884. See also Fletcher, "Preliminary Note on the Motor and Inhibitory Nerve-Endings in Smooth Muscle," *Proc. Phys. Soc., Jour. of Phys.*, vol. xxii., 1898.)

[1] Heape, "The Artificial Insemination of Mares," *Veterinarian*, 1898.

[2] See Onuf, "Notes on the Arrangement and Function of the Cell Groups in the Sacral Region of the Spinal Cord," *Jour. of Nervous and Mental Diseases*, 1899.

[3] Goltz, "Ueber das Centrum der Erectionsnerven," *Pflüger's Arch.*, vol. vii., 1873. See also Goltz and Frensberg, "Ueber die Functionen des Lendenmarks des Hundes," *Pflüger's Arch.*, vol. viii., 1874.

[4] Brachet, *Recherches expérimentales sur les Fonctions du Système Nerveux Ganglionaire*, Paris, 1839.

[5] Müller, "Klinische und Experimentelle Studien über die Innervation der Blase, etc.," *Deutsche Zeitsch. f. Nervenheilk.*, vol. xxi., 1902.

[6] Goltz (*Function d. Nervencentr. d. Froschen*, Berlin, 1869) found that in the frog the centre on which the copulation-clasp depends lies in the upper segment of the cord. Every part of the body of the female attracted the male, which would even embrace the dead female (see also Luciani, *loc. cit.*).

by sexual emotion). It is interesting to note, therefore, that Budge[1] and Eckhard[2] were able to cause the penis to erect by electrical stimulation of the cervical cord, the pons, and the crura cerebri. The same result was obtained by Pussep by exciting a definite region in the cerebral cortex. In this case erection was followed by ejaculation.[3]

It is stated also that hanging and decapitation in man are sometimes followed by erection.[4] According to Spina,[5] who experimented on the guinea-pig, section of the spinal cord, near the last costo-vertebral articulation, is invariably succeeded by erection and ejaculation.

There are certain facts which seem to show that the higher nerve centres exercise an inhibitory influence over the sexual processes. Thus, Retterer[6] states that it is easier to induce erection by external irritation in a dog whose spinal cord has been cut through, than in a normal animal.

Eckhard[7] was the first to show that the penis in the dog could be induced to erect experimentally by the stimulation of certain nerves which he called the nervi erigentes. These nerves, which are truly vaso-dilator, were found in the dog to arise from the 1st and 2nd sacral nerves, and in some cases from the 3rd sacral nerve also. Gaskell[8] showed that in the rabbit the erector fibres leave the spinal cord by the anterior (and not by the posterior) roots of the 2nd and 3rd sacral nerves. Morat[9] also found that in the dog these fibres are contained only in the anterior roots of the 1st and 2nd sacral nerves.

The corresponding parts in the female are similarly innervated. Thus, Langley[10] has described stimulation of the sacral nerves in the vertebral canal of the rabbit as producing dilatation and flushing of the vulva. These effects were most marked on exciting the 3rd and 4th sacral nerves. The stimulation of the 1st and 2nd sacral nerves, on the other hand, generally produced contraction and pallor. Langley obtained similar results in experiments on the male rabbit, the stimulation of the sacral nerves causing either protrusion and flushing of the penis, or else retraction and pallor.

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[1] Budge, "Ueber das Centrum genitospinale des Nervus sympatheticus," *Virchow's Archiv*, vol. xv., 1858.

[2] Eckhard, *loc. cit.*

[3] Pussep, "Ueber die Gehirnzentren der Penisekretion und des Samenergusses," *Inaug.-Dissert.*, St. Petersburg, 1902. Abstract in *Le Physiologiste Russe*, vol. iii., 1904.

[4] Götz, "Über Erektion und Ejaculation bei Erhängten," *Inaug.-Dissert.*, Berlin, 1898.

[5] Spina, "Experimentelle Beiträge zu der Lehre von der Erektion und Ejaculation," *Wiener Med. Blätter*, 1897.

[6] Retterer, Article "Erection," in Richet's *Dictionnaire de Physiologie*, vol. v., Paris, 1902.

[7] Eckhard, *loc. cit.*

[8] Gaskell, "On the Structure, Distribution, and Function of the Nerves which Innervate the Visceral and Vascular Systems," *Jour. of Physiol.*, vol. vii., 1886.

[9] Morat, "Les Nerfs Vaso-dilatateurs et la Loi de Majendie," *Arch. de Phys.*, 1890.

[10] Langley, "The Innervation of the Pelvic Viscera," *Proc. Phys. Soc.*, *Jour. of Physiol.*, vol. xii., 1891.

Nikolski[1] had previously stated that, on stimulating the anterior ramus of the nervus erigens (or the ramus from the 1st sacral) in the dog, he obtained a vaso-constrictor instead of a vaso-dilator effect, thus differing from Eckhard and other investigators.

Sherrington[2] found that in the male monkey excitation of the 2nd and 3rd sacral nerves produced moderate erection, and that of the 1st sacral only slight erection. In the female monkey the effects of stimulating the 3rd sacral were usually greater than in the case of the 2nd, while the 1st sacral produced no certain effects. Similar results were observed in experimenting on the cat, but in this animal stimulation of the 1st sacral nerve appears to have had a more marked effect.

François-Franck[3] found that the anterior ramus from the 1st sacral was capable of causing both vaso-constriction and vaso-dilatation. This investigator noticed further that both effects could be produced by stimulating the hypogastric nerves, but that the vaso-dilator action was more pronounced.

Budge[4] also described erector action from the hypogastrics in the rabbit. Langley and Anderson,[5] however, were unable to confirm this statement, but they found that the hypogastrics sometimes contained constrictor fibres for the external generative organs.

They state that they could discover no satisfactory evidence of the presence of vaso-dilator fibres in any of the upper or lumbar set of nerves. It would appear, therefore, that the vaso-dilator function is probably confined to the lower or sacral set of nerves.

Following Langley and Anderson's description, the fibres from the sacral set of nerves may be divided into two groups or classes, the visceral and the somatic. Stimulation of the visceral fibres (which run in the nervi erigentes) produces dilator effects on the vessels of the penis (and vulva), as already described. It also causes inhibition of the unstriated muscles of the penis, the retractor muscle of the penis (when present), and the unstriped muscles of the vulva (in the female). The somatic sacral nerves send motor branches to the ischio-cavernosus and bulbo-cavernosus muscles, as well as to the constrictor urethræ or deeper muscular stratum of the perineum. In the female they innervate the erector clitoridis, which represents the ischio-cavernosus, and the sphincter vaginæ, which embraces the lower end of the vagina, and is the homologue of the bulbo-cavernosus. The sacral nerves, as far as Langley and Anderson [1] were able to determine, send no visceral fibres by their somatic branches.

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[1] Nikolski, *loc. cit.*

[2] Sherrington, "Notes on the Arrangement of some Motor Fibres in the Lumbo-Sacral Plexus," *Jour. of Physiol.*, vol. xiii., 1892.

[3] François-Franck, *loc. cit.*

[4] Budge, *loc. cit.*

[5] Langley and Anderson, "The Innervation of the Pelvic and Adjoining Viscera," *Jour. of Physiol.*, vol. xix., 1895.

The same investigators found that stimulation of the upper or lumbar set of nerves produced strong contraction of the vessels of the penis,[2] as well as contraction of the retractor muscle, and of the other unstriated muscles of the penis, prepuce, and scrotum (dog, cat, and rabbit). The penis underwent marked retraction as a result of the excitation. Stimulation of the 2nd lumbar nerves in the cat generally produced a slight but distinct action on the external generative organs. The 3rd, 4th, and 5th lumbar nerves in many cases had a strong action, but the 6th had no action. The 1st lumbar and 13th thoracic were found to have a slight action. In the dog stimulation of the 5th lumbar nerve had no effect upon the generative organs, but the 1st lumbar was observed to have a distinct action, and also the 13th and 12th thoracic. In the rabbit no effect was produced by stimulating the 1st lumbar nerve. The 2nd lumbar had a slight action occasionally, but the 3rd, 4th, and 5th lumbar nerves always had an effect which was more or less pronounced.

The fibres from the lumbar nerves run in the white rami communicantes to the sympathetic chain, where they take two routes. (*a*) The majority of the fibres take the course of the pudic nerves (nervi pudendi). They follow the sympathetic chain to the sacral ganglia, from which fibres are given off, and these run in the grey rami communicantes to the sacral nerves. Their further course is by way of the pudic nerves (*i.e.* in the somatic branches), none apparently running in the nervi erigentes (*i.e.* to the visceral branches). (*b*) The second of the courses taken by the lumbar nerve fibres is that by the pelvic plexus. Only a relatively small number, however, take this route. Most of them run in the hypogastric nerves, but a few may join the plexus from the lower lumbar or upper sacral sympathetic chain, or from the aortic plexus. Of these latter, some may join the first root of the nervus erigens, and proceed with it to the pelvic plexus.[3]

It has already been mentioned that the clitoris in the female, like the penis, undergoes erection during coitus. The same is the case with the other parts of the vulva which contain erectile tissue. The friction which is set up between these structures and the glans of the penis causes a reflex discharge of motor impulses in both the female and the male. In the female the uterus undergoes a series of peristaltic contractions, by means of which the semen is sucked into its cavity (see p. 173). Moreover, Bartholini's glands show an increased activity and pour out a viscid secretion. In the male, the sexual impulses culminate in the emission of the semen. This is brought about by a series of muscular contractions, which probably begin in the walls of the vasa efferentia and pass to the canal of the epididymis, and thence along the vas deferens on either side. The vesiculæ seminales contract simultaneously, expelling their contents into the vasa, and the mixed fluid passes out through the ejaculatory ducts into the prostatic portion of the urethra. The prostatic muscles also contract, and probably assist in forcing the semen along the urethra, while at the same time expelling the secretion of the prostate glands. Entrance to the bladder is prevented by the erection of the crista urethræ, assisted by the contraction of the sphincter of the bladder, as already mentioned. The final discharge is brought about by the rhythmical contractions of the bulbo-cavernosus and ischio-cavernosus muscles, which have the effect of emptying the canal from behind forwards, and so ejecting the semen, mixed with the various glandular secretions, into the vaginal passage of the female.

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[1] Langley and Anderson, *loc. cit.*

[2] Vaso-constrictor fibres for the penis were first found by Eckhard (*loc. cit.*) in the nervus dorsalis penis.

[3] Langley and Anderson, *loc. cit.*

The innervation of the muscles of the penis has already been described.

The secretory cells of Cowper's glands receive branches from the pudic nerves.

The prostate is innervated by fibres coming both from the nervi erigentes and from the hypogastric nerves. The former are purely motor, whereas the latter are both motor and secretory. Eckhard[1] found that stimulation of the nervi erigentes in the dog caused the expulsion of the prostatic secretion into the urethra. Loeb[2] obtained contraction of the prostatic vesicles by excitation of the hypogastric nerves. Mislawsky and Bormann[3] confirmed both these observations, and found also that stimulation of the hypogastrics, while inducing the muscles to contract, at the same time promoted secretory activity in the glandular cells, the secretion continuing so long as the stimulation was kept up.[4] Fogge also states that he found hypogastric stimulation to produce contraction of the prostatic muscles.[1]

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[1] Eckhard, *loc. cit.*

[2] Loeb (M.), "Beiträge zur Bewegung des Samenleiters," *Inaug.-Dissert.*, Giessen, 1866.

[3] Mislawsky and Bormann, "Die Secretionsnerven der Prostata," *Zentralbl. f. Phys.*, vol. xii., 1898.

[4] Timofeew has described end-bulbs in the prostate, testis, and other male genital organs. Some of these are of a peculiar kind, and are in connection with two nerve fibres ("Zur Kenntniss der Nervenendigungen in den Männlichen Geschlechtsorganen der Säuger," *Anat. Anz.*, vol. ix., 1894).

Akutsu[2] has shown that the vesiculæ seminales in the guinea-pig receive fibres (motor as well as secretory) by the hypogastric nerves. The fibres leave the spinal cord in the 2nd, 3rd, and 4th lumbar nerves.

Budge[3] showed that it was possible to induce contraction of the vasa deferentia by stimulating the spinal cord at the level of the 4th lumbar vertebra. He observed also that contraction could be caused by stimulating one of the sympathetic ganglia, apparently the inferior mesenteric.[4]

According to Rémy,[5] stimulation of a small ganglion situated on the inferior vena cava at the level of the renal veins in the guinea-pig produced a sudden ejaculation.

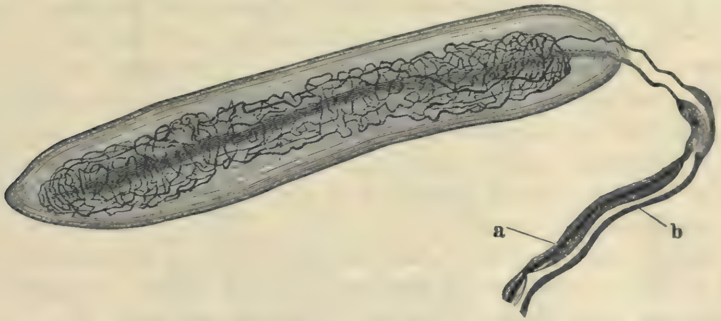

Fig. 74.—End-bulb in prostate. (After Timofeew, from Nagel.)
a, Thick medullated nerve fibre ; *b*, fine medullated nerve fibre.

Loeb[6] states that he was able to induce contraction of the vasa deferentia by stimulating the hypogastric nerves.

Langley[7] found that most of the efferent fibres for the vasa deferentia traversed the sympathetic in the region of the 4th, 5th, and 6th lumbar ganglia, so that presumably they chiefly arose from the 3rd, 4th, and 5th lumbar nerves. Sherrington[8] observed that in the macaque monkey (*Macacus rhesus*) the 2nd and 3rd lumbar nerves, and in the cat the 3rd and 4th lumbars, contained motor fibres for the vasa deferentia. The fibres giving this result could be found outside the spinal cord in the genito-crural nerve. The contraction of the vasa was of a slow and peristaltic kind, and did not cease immediately the stimulus was withdrawn.[1]

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[1] Fogge, "On the Innervation of the Urinary Passage in the Dog," *Jour. of Physiol.*, vol. xxviii., 1902.

[2] Akutsu, "Beiträge zur Kenntniss der Innervation der Samenblase beim Meerschweinchen," *Pflüger's Archiv*, vol. xcvi., 1903.

[3] Budge, *loc. cit.*

[4] Langley and Anderson, *loc. cit.*

[5] Rémy, "Nerfs éjaculateurs," *Jour. de l'Anat. et de la Phys.*, vol. xxii., 1886.

[6] Loeb, *loc. cit.*

[7] Langley, *loc. cit.*

[8] Sherrington, *loc. cit.*

Langley and Anderson, as a result of an extensive series of experiments, conclude that the internal generative organs of the cat and rabbit are supplied by fibres running out by the anterior roots of the 3rd, 4th, and 5th lumbar nerves, and sometimes also the 2nd. These fibres pass through the sympathetic to the inferior mesenteric ganglia, and continue their course by the hypogastric nerves. Stimulation of these fibres in the cat and the rabbit caused strong contraction of the whole musculature of the vasa deferentia and uterus masculinus (which Langley and Anderson regard as the physiological homologue of the vesiculæ seminales in these animals). The vas deferens in contracting was observed to become from one to three centimetres shorter, so that there could be no doubt that the longitudinal muscular coat took part in the process. The contraction was strong enough to cause emission of semen from the aperture of the penis. It would appear, therefore, that ejaculation occurred without erection. In the dog, in which the longitudinal muscle layer is not well developed, the contraction of the vas deferens, on excitation of the upper lumbar nerves, was not nearly so pronounced.

Langley and Anderson found that stimulation of the sacral nerves had no effect on the internal generative organs. These are innervated exclusively from the lumbar nerves, as above described.[2]

In view of the facts which have been related, it would appear that ejaculation is a reflex act of some complexity involving more than one centre in the spinal cord. The centre for the final expulsion of the semen must be the same as that for erection, since the muscular mechanisms concerned are to a large extent identical in each case. The centre presiding over the internal generative organs is apparently in the lumbar spinal cord. As already mentioned, Brachet observed ejaculation after all connection with the higher centres had been cut off. The centripetal nerves for the ejaculatory reflex are the sensory nerves of the penis, the stimulation of the glans being particularly effective.[1]

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[1] There has been some disagreement as to whether the vas deferens undergoes true peristaltic movement. According to Budge (*loc. cit.*) this does occur in the rabbit and cat. Fick confirmed Budge for these animals ("Ueber das Vas deferens," *Müller's Archiv*, 1856), but found no peristalsis in the dog (*cf.* Langley and Anderson for the dog). On the other hand, Loeb (*loc. cit.*) could discern no peristaltic movement in the vas deferens of the rabbit, but only a powerful contraction. Nagel, who has more recently investigated the question, states that the vas deferens in the rabbit does not undergo a true peristaltic movement, but a simple quick contraction which suffices for the emptying the tube ("Contractilität und Reizbarkeit des Samenleiters," *Verhandl. d. Phys. Gesell. zu Berlin*; *Arch. f. Anat. u. Phys.*, Phys. Abth., 1905, Suppl. See also Nagel, *Handbuch der Phys. des Menschen*, vol. ii., Braunschweig, 1906).

[2] Langley and Anderson, *loc. cit.* That stimulation of the fibres which supply the vas deferens in rabbits causes expulsive movements, without giving rise to erection, was shown by M. Loeb, *loc. cit.*

Erection has been observed to occur in animals which were castrated late in life, sexual desire in such cases being to some extent retained. It has been shown, however, that erection cannot be induced experimentally in animals which have been castrated prior to puberty; or, at any rate, that it is far more difficult to cause erection in such animals. Thus, in three experiments carried out by the writer, in conjunction with Professor Sutherland Simpson,[2] it was

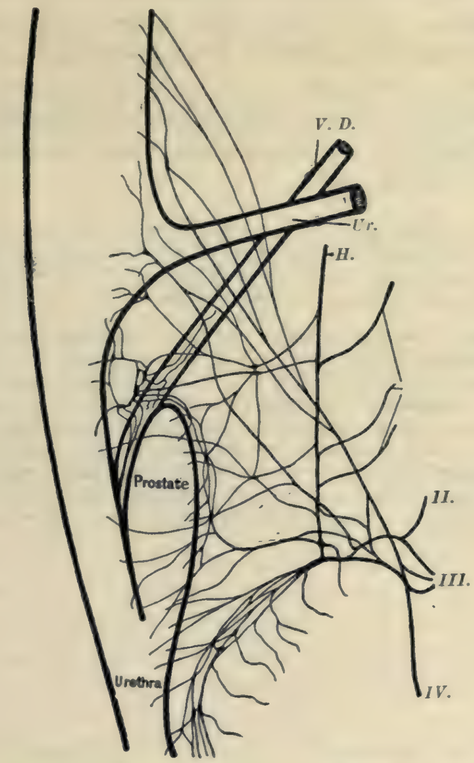

Fig. 75.—Diagram illustrating innervation of internal genital organs of male cat. (From Nagel.)

H., Hypogastric nerve; *Ur.*, ureter; *V. D.*, vas deferens; II., III., IV., branches arising from 2nd, 3rd, and 4th lumbar nerves.

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[1] For further references to the literature of the nervous mechanism of erection and ejaculation, see Bechterew, *Die Funktionen der Nervencentra*, Weinberg's German Translation, vol. i., Jena, 1908.

[2] Simpson and Marshall, "On the Effect of Stimulating the Nervi Erigentes in Castrated Animals," *Quar. Jour. Exper. Phys.*, vol. i., 1908.

found impossible to induce erection by stimulating the nervi erigentes in three cats which were castrated when about half grown and afterwards allowed to reach their full size. It is possible, therefore, that in such animals the muscular apparatus of the penis fails to develop sufficiently to admit of erection occurring, but it would seem unlikely that the nervous mechanism is impaired. If erection is due mainly to an inhibition of the vaso-motors of the penis, as is ordinarily supposed, there would seem to be no theoretical reason why it should not be possible to bring about that process experimentally in castrated animals. It is conceivable, therefore, that the process of erection is after all a more complex phenomenon than is generally believed, but our experiments throw no further light on the mechanism of that process.[1]

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[1] Ott and Scott (*Contributions from Laboratory of Medico-Chirurgical College of Philadelphia*, 1912) state that injection of prostatic extract causes erection, the length of the penis and the breadth of the bulb being considerably greater than after injection of testicular, ovarian, parathyroid, or pituitary extracts.

[Note to p. 262. The reproductive organs of bats, and the evidence as to their manner of copulation are described by Wood Jones ("The Genitalia of the Cheiroptera," *Jour. of Anat.*, vol. li., 1917). The process appears to occur while the animals are suspended. (See also Wood Jones, *Jour. of Anat.*, vol. li., for genitalia of *Tupaia.*) Meek has given an account of the genital organs in the Cetacea. In the porpoise (*Phocæna communis*) the penis consists of two portions, proximal and terminal; during erection the terminal part remains pliable and takes on a corkscrew-like movement, the proximal part becoming hard and rigid ("The Reproductive Organs of the Cetacea," *Jour. of Anat.*, vol. lii., 1918).]

CHAPTER VIII[1]

THE BIOCHEMISTRY OF THE SEXUAL ORGANS

> "Nous sommes dans un de ces châteaux des légendes allemandes où les murs sont formés de milliers de fioles qui contiennent les âmes des hommes qui vont naître. Nous sommes dans le séjour de la vie qui précède la vie."—MAETERLINCK, *La Vie des Abeilles.*

THE FEMALE GENERATIVE ORGANS

Mammals

IN Mammals very little is known concerning the chemistry of the female generative organs. The difficulty experienced in obtaining material has rendered impossible a chemical investigation of the ovum itself. The fluid contained in the Graafian follicles of the cow is stated to be of a serous nature. From the corpora lutea of the same animal amorphous and crystalline pigments have been isolated, both of which belong to the class of substances called lipochromes or luteins.[2] These pigments are also found in other sites, *e.g.* in adipose tissue, in serum, in the retina, and in milk. Similar pigment substances have been isolated from plants. In fact, the later work of Escher[3] has shown that the crystalline pigment obtained from the corpora lutea is a hydrocarbon of the formula $C_{40}H_{56}$ and is identical with the pigment carotin[4] obtained from plants. The luteins are not related to blood pigment, and although hæmatoidin may be found in corpora lutea, especially when they are fresh, the existence of the luteins appears to be quite independent of the presence of blood pigments. The luteins contain carbon and hydrogen and have a yellowish or reddish colour. Exposed to light they undergo oxidation. They are soluble in alcohol, ether, and chloroform, and in that respect resemble fats, from which they differ, however, in their resistance towards alkalis. With strong nitric acid and sulphuric acid they give a blue colour. Their solutions in alcohol, ether, or chloroform are further characterised by the absorption-spectrum,[1] which shows two bands in the blue part of the spectrum (between the lines F and G). The luteins are usually associated with the fatty substances, *i.e.* true fats and lipoids, in their distribution. The corpus luteum is rich in fatty substances deposited in the cells in the form of numerous relatively large globules. The morphological appearance of the lutein cells is therefore similar to that of the adrenal cortex and the glandular adipose tissue. This similarity extends to the nature of the fatty substances present. These are composed partly of true fats and partly of lipoids, among which cholesterin and its esters can be identified most readily. Phosphatides (lecithin) and cerebrosides, either free or in combination with sphingomyelin, are also present.

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[1] By William Cramer.

[2] Piccolo and Lieben, "Studi nel corpo luteo della vacca," *Giorn. Sc. Natur. ed Econ.*, vol. ii., 1866. Kühne and Ayres, "On the Stable Colours of the Retina," *Jour. of Physiol.*, vol. i., 1878.

[3] Escher, "Über den Farbstoff des Corpus luteum," *Zeitsch. f. physiol. Chem.*, vol. lxxxiii., 1912.

[4] Willstätter, chapter on "Chlorophyll" in Abderhalden's *Biochemisches Handlexikon*, vol. vi., 1911.

The estimations of Iscovesco[2] and of Chauffard[3] and his collaborators have given quantitative data from which the following table has been calculated for the sow:—

	Ovaries.		Corpus Luteum.	
	Fresh.	Dried.	Fresh.	Dried.
	Per Cent.	Per Cent.	Per Cent.	Per Cent.
Total lipoids - -	17·3	3·01	32·3	5·87
Cholesterin - -	1·22	0·35	6·32	1·15

The figures represent averages, and the individual estimations show considerable variations, since the lipoid content of the corpus luteum varies with its functional state. Chauffard and his collaborators distinguish three stages in the evolution of the corpus luteum for which they give the following average figures:—

	Cholesterin Content.
Initial hæmorrhagic stage - - -	1·99 per cent.
Mature stage - - - -	5·84 ,,
Regressive stage - - - -	10·92 ,,

Observations on the phosphatides of the corpus luteum of the sow during pregnancy[4] indicate a diminution as pregnancy advances. In the following table the figures for the P_2O_5 percentage of the alcohol-soluble lipoids have been calculated as lecithin :—

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[1] Thudichum, "Über das Lutein und die Spektren gelbgefärbter organischer Substanzen," *Centralblatt f. d. med. Wissenschaft*, vol. vii., 1869.

[2] Iscovesco, "Les lipoides de l'ovaire," *Comptes rend. Soc. de Biol.*, vol. lxxiii., 1912.

[3] Chauffard, Laroche et Grigaut, "Fonction cholesterinogénique du corps jaune," *Comptes rend. Soc. de Biol.*, vol. lxxii., 1912.

[4] Corner, "Variations in the Amount of Phosphatides in the Corpus Luteum of the Sow during Pregnancy," *Jour. Biol. Chem.*, vol. xxix., 1917.

Stage of Pregnancy.	Length of Embryo.	Lecithin Percentage in Fresh Tissue.
	Mm.	Per Cent.
Early pregnancy - - -	7-13	·71
Middle pregnancy - -	98-140	·48
Late pregnancy - - -	190-270	·44

From observations on the ovaries and corpora lutea of pregnant and non-pregnant cows Rosenbloom[1] has obtained figures from which the following table has been abstracted. The figures for cholesterin, which can be estimated very accurately, are very similar to those obtained by the French observers. The differences in the figures for the phosphatide content can be attributed largely to different methods of extraction and calculation.

Per Cent. in Dry Tissue of	Ovary.			Corpus Luteum.		
	Non-Pregnant.	Pregnant.		Non-Pregnant.	Pregnant.	
		Early.	Late.		Early.	Late.
	Per Cent.	Per Cent.	Per Cent.	Per Cent.	Per Cent.	Per Cent.
Neutral fats -	0·755	0·60	0·63	2·95	3·05	2·99
Phosphatides -	0·394	0·348	0·363	14·10	14·90	14·87
Cholesterin - -	0·446	0·40	0·437	1·09	1·09	1·17

The corpus luteum is therefore characterised by an abundance of lipoids. The interstitial cells of the ovary contain globules of similar mixtures of lipoids.

What specific functions these lipoids subserve in the sexual organs is not known, although there is no lack of speculation on the subject. From the morphological similarity of the cells of the corpus luteum and those of the adrenal cortex, an identity of function for the two organs has been postulated. But since the specific functions of the cortex of the suprarenal gland are still obscure the suggestion is more brilliant than helpful. The cells of the corpus luteum and of the adrenal cortex resemble each other as much as they resemble the cells of glandular adipose tissue,[2] which occurs scattered in circumscribed masses throughout the body, and the cells of the so-called hibernating gland. All these cells have the appearance of glandular cells in which numerous lipoid globules are deposited. It is very probable that these various groups of tissues are functionally correlated in so far as the metabolism of cholesterin and the associated lipoids is concerned, so that changes or disturbances in the cholesterin metabolism will be reflected in these various tissues. But from this to an identity of function is a far cry.

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[1] Rosenbloom, "The Lipins of the Ovary and Corpus Luteum of the Pregnant and Non-Pregnant Cow," *Jour. Biol. Chem.*, vol. xiii., 1912.

[2] Cramer, "On Glandular Adipose Tissue, etc.," *Brit. Jour. Exp. Pathol.*, vol. i., 1920, p. 184.

Observations concerning the chemistry of *human* ovaries have been made chiefly in certain pathological conditions of these organs. Various protein substances have been isolated from the fluid contents of ovarian cysts. In the case of cysts due to a dilatation of the Graafian follicles the contents were found to be identical with other serous liquids. From cystic tumours of the ovaries, the contents of which may be either watery or gelatinous, a number of protein compounds have been isolated, which, on hydrolysis, all yield a considerable quantity of a reducing substance—glucosamine—and therefore belong to the group of glycoproteins. Hammarsten[1] isolated a substance, called by him Pseudomucin, which did not coagulate on heating and was not precipitated by acetic acid. On hydrolysis it yielded thirty per cent. glucosamine. Pfannenstiel[2] isolated from ovarian colloid another mucoid substance, Pseudomucin β, a gelatinous mass which was insoluble in acetic acid and water, but was dissolved by dilute alkali. These substances are formed by the activity of the cells lining the cysts.[3]

Birds

Our knowledge of the chemistry of the ovum is derived almost entirely from investigations on the hen's egg. The average weight of an egg is 40-60 gm., half of this being the weight of the white of the egg, while the yolk weighs 12-18 gm. and the shell 5-8 gm.

The egg-shell contains chiefly calcium[4] carbonate. During development the egg-shell loses inorganic substances, especially calcium, to the amount of 0·15 gm. This goes to the building up of the structures of the developing embryo.[5] In some species the shell is coloured by pigments, which are probably allied to the bile pigments.[1] There are variations in the strength and thickness of the shells of different eggs. Sometimes they are exceptionally thin and soft. Riddle[2] holds that there is a loose association between the production of inadequate shells and the early death of the embryo before hatching. Feeding with calcium does not prevent the production of inadequate shells, so that lack of calcium cannot be its cause.

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[1] Hammarsten, "Metalbumin und Paralbumin," *Zeitsch. f. physiol. Chem.*, vol. vi., 1882.

[2] Pfannenstiel, "Über die Pseudomucine der cystischen Ovariengeschwülste," *Arch. f. Gynækologie*, vol. xxxviii.

[3] For further details concerning the chemical pathology of the ovaries see Wells' *Chemical Pathology*, 3rd Edition, 1918.

[4] Vaughan, "Estimation of Lime in the Shell and in the Interior of the Egg before and after Incubation," *Jour. of Physiol.*, vol. i., 1878.

[5] Tangl, "Untersuchungen über die Beteiligung der Eischale am Stoffwechsel des Einhalts während der Bebrütung," *Pflüger's Arch.*, vol. cxxi., 1908.

The shell membrane consists of a substance belonging to the group of the keratins. It is very rich in sulphur (about four per cent. S), and, on hydrolysis, yields a relatively large amount of cystin (see p. 288). It also loses weight during development. The loss consists of organic substances and amounts to 0·2 gm.

The chief constituents of the white and the yolk of the egg are water, proteins, fats, and phosphorised fats, while carbohydrates as such are almost entirely absent. The white of the egg contains on the average 0·47 per cent. dextrose, the yolk 0·14 per cent., while for the whole egg the average is 0·45 per cent. dextrose.[3]

The proportion in which these constituents are present in the white and in the yolk of the egg differs, as will be seen from the following table giving the total composition of both these parts. The figures for the yolk are taken mainly from Riddle's estimations.[4]

	White of Egg.	Yolk of Egg.
	Per Cent.	Per Cent.
Water - - - - - - - -	85 to 88	45·40
Protein - - - - - - -	13·0	15·04
Fat - - - - - - - -	0·3	25·25
Phosphorised fat, calculated as lecithin -	trace	11·15
Cholesterin - - - - - - -	,,	1·75
Reducing sugar - - - - - -	0·47	0·14
Inorganic salts - - - - -	0·7	0·96

Another important difference in the composition of the white and the yolk of the egg is to be found in the relative quantities of the inorganic constituents as they are present in the dry residue,[1] both as inorganic salts and in organic combination.

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[1] Krukenberg, "Farbstoffe der Vogeleierschalen," *Verhandlungen d. Phys. Med. Gesellschaft*, Würzburg, vol. xvii., 1883.

[2] Riddle, "Studies on the Physiology of Reproduction in Birds," *Amer. Jour. of Physiol.*, vol. lvii., 1921.

[3] Hepburn and St. John, "Dextrose content of the Hen's Egg," *Proc. Amer. Soc. Biol. Chemists*, 1921, *Jour. Biol. Chem.*, vol. xlvi.

[4] Riddle, "Studies on the Physiology of Reproduction in Birds," *Amer. Jour. of Physiol.*, vol. xli., 1916. This paper contains a full bibliography.

100 parts of Dry Residue of	Contain— K_2O.	Na_2O.	CaO.	MgO.	Fe_2O_3.	P_2O_5.	Cl.
White of egg	1·44	1·45	0·13	0·13	0·00	0·20	1·32
Yolk of egg	0·27	0·17	0·38	0·06	0·024	1·90	0·35

It will be seen that the yolk is distinguished by the presence of iron which is almost completely absent from the white, and by its richness in phosphorus. Although the percentage of iron present in the yolk is very small, it is nevertheless greater than in almost any other animal or vegetable food-stuff.

As a rule the proportions in which the inorganic elements are present are given in terms of percentages of the ash. Such a table,[2] which perhaps brings out more clearly the difference between the white and the yolk of the egg, may be given here:—

100 parts of the Ash of	Contain— K_2O.	Na_2O.	CaO.	MgO.	Fe_2O_3.	P_2O_5.	SiO_2.	Cl.
White of egg	31·14	31·57	2·78	2·79	0·57	4·71	1·06	28·82
Yolk of egg	9·29	5·87	13·04	2·13	1·65	65·46	0·86	1·95

There are, of course, slight variations between different eggs in the amount of mineral constituents present in the ash. It is possible that there are such variations even in the eggs laid by one and the same bird at different periods. Systematic investigations on this point have been made only with reference to the iron. These observations show that more iron is present in eggs laid in spring than in eggs laid by the same bird in autumn, the amounts varying from 0·0129 per cent. Fe_2O_3 to 0·0086 per cent. Fe_2O_3, the maximum found being 0·0167 per cent. Fe_2O_3. (The percentage is calculated for the dried yolk.) This fact probably explains the very exaggerated statements which have been made concerning the production of eggs rich in iron by keeping hens on a diet rich in iron. The careful observations of Hartung[3] show that there is indeed a distinct effect produced by such a diet, provided that it is given over a prolonged period—two months or more. But the effect of such a diet is limited, and does not go beyond the physiological maximum. The percentage of iron present in eggs laid under these conditions remains fairly constant, and is about equal to the maximum found under normal conditions, namely 0·0165 per cent. Fe_2O_3, so that the seasonal diminution which normally appears is prevented.

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[1] Bunge, "Der Kalk und Eisengehalt unserer Nahrung," *Zeitsch. f. Biologie*, vol. xlv., 1904, p. 532.

[2] Albu and Neuberg, *Physiologie und Pathologie des Mineralstoffwechsels*, Berlin, 1906, p. 241.

[3] Hartung, "Der Eisengehalt des Hühnereies," *Zeitsch. f. Biologie*, vol. xliii., 1902.

The phosphoric acid constitutes more than half of the ash of the yolk, and it is interesting to note that both the phosphorus and the iron, which are destined to enter into the composition of some of the most important constituents of the cell, such as nucleoproteins, hæmoglobin, lipoids, etc., are already present in organic combination. The phosphorus is contained in the phosphorised fats, which constitute about eleven per cent. of the yolk, and partly in the phosphoprotein vitellin, which also contains iron.

The phosphorised fats are obtained by extracting the yolk, which has previously been freed from water, with cold ether, and precipitating the ethereal extracts with acetone. The precipitate contains the phosphorised fats, while the acetone solution contains the cholesterin which has been extracted together with the phosphorised fats. After all the ether-soluble phosphorised fats have been removed by the ether, further extraction with cold alcohol will remove other phosphorised fats from the yolk.

The precipitate obtained from the ethereal extract by acetone has often been called lecithin, the name given to the simplest and best-known phosphorised fat. But the work of Erlandsen,[1] and of Thierfelder and Stern,[2] has shown, what in the case of nervous tissue had been recognised long ago by Gamgee and by Thudichum, that there are a number of phosphorised fats very similar to lecithin and very difficult to separate from each other. These substances, accompanied always by cholesterin, are widely distributed through the organic world. In fact they are present in every cell, and in almost every animal fluid. This fact alone is sufficient to indicate that the phosphorised fats and cholesterin must fulfil an important function in the life of the cell.

What this function is has not yet been clearly recognised. We know that anæsthetics such as chloroform, and toxins such as snake-venom, exert their action on the cell by virtue of the power of the phosphorised fats to absorb these substances. Lecithin also absorbs or adsorbs sugars, and the resulting sugar-containing adsorption complex is soluble in ether, while pure sugars are not. Ethereal solutions of lecithin take up with great avidity dyes, such as brilliant green, methyl violet, which are soluble in water, but not in ether, and the resulting lecithin dye complex has then the solubilities of a lipoid.[3] Many inorganic salts and alkaloids such as quinine are also adsorbed by lecithin. Lecithin also absorbs oxygen very readily and becomes oxidised even at room temperature. It has, therefore, many of the properties which we associate with living protoplasm; it may be said to absorb food-stuffs and to assimilate them in the sense of altering the properties of these food-stuffs; it shows selective staining and it absorbs oxygen. Some experiments of the writer,[1] carried out in 1908, suggest that these phosphorised fats may act as oxygen-carriers, and that they may thus fulfil an important function in cell-respiration. A similar view has been put forward also on purely theoretical grounds by Mansfeld.[2]

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[1] Erlandsen, "Untersuchungen über die lecithinartigen Substanzen des Herzmuskels," *Zeitsch. f. physiol. Chem.*, vol. li., 1906.

[2] Thierfelder and Stern, "Über die Phosphatide des Eigelbs," *Zeitsch. f. physiol. Chem.*, vol. liii., 1907. For detailed information see the review of Levene, "Structure and Significance of the Phosphatids," in *Physiological Reviews*, issued by the American Physiological Society, Baltimore, 1921.

[3] Cruikshank, "The Adsorption of Dyes and Inorganic Salts by Solutions of Lecithin," *Jour. of Pathol.*, vol. xxiii., 1920, p. 230.

However that may be, there can be little doubt that in the egg, which contains an exceptionally large amount of phosphorised fats, these substances have to fulfil a different function. Phosphorus enters into the composition of many cell constituents, for instance the complex protein substances found in the nuclei of cells, the so-called nucleoproteins, so that the assimilation of phosphorus is an important factor in the growth of an organism. In birds the yolk of the egg fulfils a function similar to that of the milk in Mammals; both supply the offspring with the material necessary for its growth. We thus find that both the yolk and the milk are not only rich in phosphorus, but that most of the phosphorus is present in organic combination, as casein and nuclein in the latter, and as vitellin and phosphorised fats in the former.

It was held at one time that the organism could not synthesise organic phosphorus compounds from inorganic phosphates. This has been disproved by Gregersen,[3] who showed that animals can maintain themselves in phosphorus equilibrium when inorganic phosphates are the only source of phosphorus, provided that protein is also given. Similarly the eggs of ducks fed on a diet containing only inorganic phosphates were found to have a normal lecithin value.[4] It is therefore not very obvious why both egg-yolk and milk should be so rich in organic phosphorus compounds: it may be merely to lighten the work of synthesis laid upon the cells of the embryo. In any case it is certain that the mother synthesises organic phosphorus compounds for the offspring. In birds it has been shown[1] that the blood of laying hens is much richer in phosphorised fats than that of non-laying hens or of male birds. This indicates that these substances are transported in the laying hen from their depots to the egg, and this transport is associated with the disappearance of the yellow colour from the body, especially the beak, legs, and anus, the natural colour for the Leghorns and all American breeds. Thus, birds with pale legs, beaks, and ani, are stated to have a high average egg production and their blood is rich in fatty substances. The converse is said to hold true for hens with distinctly yellow legs, beaks, and parts surrounding the anus.[2]

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[1] Cramer, Unpublished observations. It was found that watery emulsions of egg-lecithin absorbed much more oxygen than water alone or watery solutions of proteins, and that such a lecithin-emulsion sometimes greatly accelerated the oxidation of hydriodic acid by the oxygen of the air. The results obtained were, however, very variable. Thunberg (*Skandin. Arch. f. Physiol.*, vol. xxiv., 1911) has since shown that the absorption of oxygen by watery lecithin emulsion is greatly increased by the presence of minute traces of iron (1 : 6,000,000).

[2] Mansfeld, "Narkose und Sauerstoffmangel," *Pflüger's Arch.*, vol. cxxix., 1909.

[3] Gregersen, "Untersuchungen über den Phosphorstoffwechsel," *Zeitsch. f. physiol. Chem.*, vol. lxxi., 1911.

[4] Fingerling, "Die Bildung von organischen Phosphorverbindungen aus anorgischen Phosphaten," *Biochem. Zeitsch.*, vol. xxxviii., 1912. M'Collum, Halpin, and Drescher, "Synthesis of Lecithin in the Hen," *Jour. Biol. Chem.*, vol. xiii., 1912.

The yellow pigmentation is due to a lutein which is associated with the fatty substances both of the adult fowl and of the yolk. It was isolated in crystalline form by Willstätter and Escher,[3] had the composition $C_{40}H_{56}O_2$, and found to be closely allied to, if not identical with, the plant pigment xanthophyll. It is slightly different from the lutein of the mammalian ovum.

During incubation the vitellin disappears and the phosphorised fats diminish, so that at the twentieth day their quantity is reduced by one-half.[4] It is, of course, clear that the formation of nucleoproteins cannot account for this enormous consumption of phosphorised fats. Some of these substances reappear in the embryo. A proportion of them contributes to the formation of bones, which contain a considerable amount of inorganic phosphates; part reappears in the fœtal tissues as phosphorised fats, especially in the nervous tissue, which is very rich in these substances. That portion of the phosphorised fats which is transformed into inorganic phosphates may at the same time fulfil another very important function by the oxidation of the fat group in their molecule. It will be shown below that the development of the embryo is intimately associated with, and perhaps dependent upon, the transformation of chemical energy into heat. This transformation is brought about by the oxidation of certain organic substances, which are different in the different classes of Vertebrates. It will be shown also that in birds the chemical energy is furnished by fats; and it is very probable that the phosphorised fats furnish at the same time material for the formation of the tissues of the embryo and fat as a source of chemical energy.

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[1] Lawrence and Riddle, "Sexual Differences in the Fat and Phosphorus of the Blood of Fowls," *Amer. Jour. of Physiol.*, vol. xli., 1916.

[2] Warner and Edmond, "Blood Fat in Domestic Fowls in Relation to Egg Production," *Jour. Biol. Chem.*, vol. xxxi., 1917.

[3] Willstätter and Escher, "Über das Lutein des Hühnereidotters," *Zeitsch. f. physiol. Chem.*, vol. lxxvi., 1912.

[4] Merconitzki, "Die quantitativen Veränderungen des Lecithins im enstehenden Organismus," *Russky Wratsch*, 1907, quoted from *Biochemisches Centralblatt*, vol. vi., 1907. Plimmer and Scott, "The Transformations in the Phosphorus Compounds in the Hen's Egg during Development," *Jour. of Physiol.*, vol. xxxviii., 1909. Riddle, "Metabolism of the Yolk during Incubation," *Amer. Jour. of Physiol.*, vol. xli., 1916; also *Jour. of Morphology*, vol. xxii., 1911.

It is interesting to note that a similar double function has been assigned to glycogen in the case of the developing rabbit.[1] Of the cholesterin present in the fresh egg about one-third disappears during incubation. The remainder reappears in the embryo.

The phosphorus which enters into the composition of nucleoprotein is bound up therein in the form of phosphoric acid, combined with purine bases and sugars (pentoses or hexoses) (see p. 307). Neither nucleoprotein nor sugars are present in the fresh egg, and purine bases are present only in very small amounts. The fact that during development these substances rapidly increase in amount indicates, therefore, that a synthesis, not only of nucleoprotein, but also of some of its constituent groups from the reserve material of the egg (proteins and phosphorised fats), takes place during development.[2] The purine bases found in the embryo are essentially the same as those found in the adult organism.

Of the phosphorised fats of the yolk, lecithin is the simplest and best-known representative. Like all fats, it is an ester, a compound of glycerine and fatty acids, some saturated, as stearic and palmitic acids, others unsaturated, as oleic acid. Like all fats, it is soluble in alcohol and ether. With water it swells up and forms a colloidal solution. It is distinguished by the presence in its molecule of one molecule of phosphoric acid to which one molecule of an organic nitrogenous base, choline, is attached. If boiled with baryta water it is decomposed into glycerophosphoric acid, fatty acids, and choline. Lecithin forms loose compounds with proteins, the so-called lecithalbumins, of which vitellin is probably one.

Vitellin is an ill-defined compound between lecithin and a protein substance which itself contains about one per cent. phosphorus. It is insoluble in water, but soluble in dilute solutions of neutral salts, behaving in that respect like a globulin. On peptic digestion a pseudonuclein, rich in phosphorus, is formed from the protein part of vitellin. This pseudonuclein contains also a relatively large amount of iron in organic combination, and it is this substance which is responsible for the presence of iron in the yolk of the egg. According to Bunge,[1] this substance plays an important part in the formation of hæmoglobin in the chick. It is the precursor of hæmoglobin, and has, therefore, been called by him hæmatogen. It contains 5·19 per cent. P and 0·29 per cent. Fe. Plimmer[2] has isolated from egg-yolk another protein, livetin, soluble in water and containing 0·1 per cent. phosphorus.

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[1] Lochhead and Cramer, "The Glycogenic Changes in the Placenta and Fœtus of the Pregnant Rabbit," *Proc. Roy. Soc.*, Series B, vol. lxxx., 1908.

[2] Kossel, "Weitere Beiträge zur Chemie des Zellkernes," *Zeitsch. f. Physiol. Chem.*, vol. x., 1886. Mendel and Leavenworth, "Chemical Studies on Growth: VI. Changes in the Purine- Pentose- and Cholesterol-Content of the Developing Egg," *Amer. Jour. of Physiol.*, vol. xxi., 1898. Fridericia, "Untersuchungen über die Harnsäureproduktion und die Nucleoproteid neubildung beim Hühnerembryo," *Skandin. Arch. f. Physiol.*, vol. xxvi., 1912.

Two different fats have been isolated from the yolk—the one solid, rich in palmitic acid; the other fluid, containing equal parts of palmitic and oleic acids. A small amount of stearic acid is also present in both fats. The composition of the fatty substances is influenced by the food. According to Henriques and Hansen[3] the fat of the food passes into the yolk in the same kind of way as it passes into the fat deposits of the adult organism. The observations of M'Collum and his collaborators[4] have given the extraordinary result that the lecithins of the egg-yolk do not possess a specific composition, but that they are variable in respect of the nature of the fatty acid radicals which they contain, and that these can be made to vary by varying the food.

The food has also an influence upon the colour of the yolk, which is due to luteins. Feeding with grains produces a light yellow yolk, a dark yellow yolk results if grass and herbs are given, while feeding with worms leads to the production of an even darker reddish yolk. What the changes are in the colouring matter of the yolk has not yet been ascertained.[5]

During the development of the chick a considerable portion of the fat disappears. In other words, a certain amount of chemical energy, which in the fresh egg is present in the form of fat, disappears. Liebermann[6] has shown, for instance, that of 5·4 gm. of fat present in a fresh egg only 2·7 gm. can be recovered when the chick is hatched. The fate of the chemical energy which has thus disappeared has been accounted for completely by the observations of Bohr and Hasselbalch,[7] which are the most exact and comprehensive investigations on the subject of the metabolism of the embryo.

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[1] Bunge, "Über die Assimilation des Eisens," *Zeitsch. f. physiol. Chem.*, 1884, vol. ix.

[2] Aders Plimmer, "The Proteins of Egg-Yolk," *Jour. Chem. Soc.*, 1908.

[3] Henriques and Hansen, "Über den Übergang des Nahrungsfettes in das Hühnerei," *Skandin. Arch. f. Physiol.*, vol. xiv., 1903.

[4] M'Collum, Halpin, and Drescher, "Synthesis of Lecithin in the Hen," *Jour. Biol. Chem.*, vol. xiii., 1912.

[5] For the morphological distribution of the constituents of the yolk, see Waldeyer, "Die Geschlechtszellen," in Hertwig's *Handbuch der Entwicklungslehre der Wirbeltiere*, vol. i., Jena, 1903.

[6] Liebermann, "Embryochemische Untersuchungen," *Pflüger's Arch.*, vol. xliii., 1888.

[7] Bohr and Hasselbalch, "Über die Wärmeproduktion und den Stoffwechsel des Embryo," *Skandin. Arch. f. Physiol.*, vol. xiv., 1903.

The developing egg takes in oxygen and gives off CO_2. Bohr and Hasselbalch showed that the respiratory quotient of the developing egg—that is, the ratio of the amount of CO_2 excreted to the amount of O_2 absorbed—is 0·71. Such a quotient indicates the oxidation of fat. From the amount of CO_2 excreted during a given period it is possible to calculate the amount of fat oxidised during that period. Under ordinary conditions the oxidation of fat produces heat which can be determined experimentally. By calculating from the amount of fat oxidised during development the amount of heat which would be generated under ordinary conditions, and by actually determining at the same time the amount of heat given off by the developing egg, Bohr and Hasselbalch found during a period of twelve days:—

The amount of heat calculated from the amount of fat oxidised -	12·11 Cals.
„ „ actually given off - - - - -	12·16 „

This remarkable agreement in so complicated an experiment—which is a triumph of the experimental skill of the observers—shows clearly that fat is the almost exclusive source of the chemical energy which is used up during development. Another very important conclusion can be drawn from these observations, namely, that all the chemical energy which disappears during development reappears in the form of heat; none is transformed in an unknown way into energy of a different kind, or transferred to the developing embryo.

This observation, which is of fundamental importance in its bearing on our conceptions of life and living matter, was confirmed by Tangl. The converse was also experimentally tested by Rubner[1] in the case of yeast. When yeast-cells undergo autolysis no energy is liberated. These experimentally established facts dispose in a final and conclusive manner of all speculations concerning the existence of unknown forms of energy in living cells.

The intensity of the metabolic changes which take place during development, and which can be expressed by the amount of CO_2 excreted, is very great.[2] Calculated for the same unit of weight of the animal, it is as great in the embryo as it is in the adult animal, and may even exceed it. This is the case not only in birds, but also in Mammals. These changes are bound up with the development of the embryo. Exposure to cold, which delays development, also diminishes the excretion of carbonic acid.[3] Experiments on the eggs

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[1] Rubner, "Die Umsetzungswärme bei der Alkoholgärung," *Arch. f. Hygiene*, vol. xlix.

[2] Bohr and Hasselbalch, "Über die Kohlensäureproduktion des Hühnerembryos," *Skandin. Arch. f. Physiol.*, vol. x., 1900.

[3] Pembrey, "On the Response of the Chick, before and after Hatching, to Changes in External Temperature," *Jour. of Physiol.*, vol. xxvii., 1894.

of cold-blooded animals[1] show that those conditions which favour development, such as high temperature, also lead to an increase in the CO_2 excretion. But the relation between oxygen consumption and development is not a simple one. For as J. Loeb has shown in the parthenogenetic development of unfertilised eggs the oxygen consumption increases before the actual development begins. And Warburg[2] found that one can prevent the segmentation of the egg without diminishing the respiration.

The problem of the energy exchange during development has been attacked in a different way by Tangl.[3] He determined, by means of a calorimeter, the heat produced by the combustion of eggs at different stages of their development. There is a gradual diminution of the caloric value as development goes on, indicating that chemical energy is used up in the process of development. For the chick the following "balance-sheet" can be drawn up from the observations of Tangl and his collaborators. The caloric value of an egg of average weight (54 gm.) is 87 Cals. The difference between the caloric value of the fresh egg and that of the incubated egg is 23 Cals. These 23 Cals. represent the chemical energy which has been used up for what Tangl calls the "work of development." Calculated for 1 gm. of chick this amounts to 805 small calories.

Before Incubation.		*After Incubation.*	
Caloric value of egg	87 Cals.	Transformed into heat	23 Cals.
		Present in body of developed chick	38 „
		Remaining unused	26 „
Total	87 Cals.	Total	87 Cals.

But since Bohr's work has shown that the chemical energy which disappears during development is completely transformed into heat, it would be better to replace the term "work of development" by the term "energy of development."

The nature of the substances which by their oxidation furnish the "energy of development" is different in the different classes of animals. In birds it is furnished, as we have seen, by the oxidation of fats, and possibly also of the fatty group of the phosphorised fats. In Mammals, in which development proceeds *in utero* and there is a constant exchange of material between the mother and the fœtus, the investigation of these problems is more difficult, owing to the complexity of the conditions. Investigations on the respiratory quotient of the embryo in pregnant guinea-pigs and rabbits[1] indicate that there is an oxidation of carbohydrate material, and systematic chemical investigations of the placenta and fœtus of pregnant rabbits[2] have shown that there is a constant and regular disappearance of glycogen from the placenta, which reappears only partly as such in the embryonic tissues. It can, therefore, be concluded that in these animals glycogen furnishes at least part of the "energy of development." But it is doubtful whether this conclusion can be applied to all the Mammals, since in the case of the cow and of the sheep very little glycogen is found in the placenta.

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[1] Bohr, "Über den respiratorischen Stoffwechsel beim Embryo kaltblütiger Tiere," *Skandin. Arch. f. Physiol.*, vol. xv., 1904.

[2] Warburg, "Untersuchungen über die Oxydationsprocesse in Zellen," *Münchener Mediz. Wochenschr.*, 1912, p. 2550.

[3] Tangl, "Beiträge zur Energetik der Ontogenese: I. Die Entwicklungsarbeit im Vogelei," *Pflüger's Arch.*, vol. xciii., 1903; vol. cxxi., 1908.

In reptiles[3] also the chemical energy used up during development is furnished mainly by carbohydrates.

Similar observations have been made on the eggs of fishes,[4] where the energy of development was found to be very small.

In all these cases the chemical energy used up in the process of development has been found to be furnished either by fats or by carbohydrates. No conclusive evidence has as yet been obtained that the store of nitrogenous substances is used for energetic purposes. Nor is it at all clear what changes the protein substances of the egg undergo during development.[5]

Liebermann records a loss of nitrogenous substances in his analysis of hens' eggs at various stages of development; but as Hasselbalch[6] pointed out, this loss is accounted for by the egg-membrane, which is left behind when the chick is hatched, and which was not included in Liebermann's analysis.

Reference has already been made to the nitrogenous constituents of the yolk; the two phosphoproteins vitellin and livetin. The other protein substances of the white of the egg can be distinguished according to their reactions as albumens, globulins, and a substance behaving like a peptone in so far as it is not coagulated by heat and not precipitated by ammonium sulphate or by hydrochloric and acetic acids. According to the investigations of Mörner,[7] this substance is a true glucoprotein and belongs to the mucoid substances. It has, therefore, received the name Ovomucoid. On boiling with hydrochloric acid it yields 34 per cent. of glucosamine.[1] The ovomucoid present in the white of the egg amounts to about 10 per cent. of the proteins; 6 per cent. of the proteins belong to the globulin group, the remainder being the albumens. All the proteins of the white of the egg, not only the ovomucoid, are exceptionally rich in the carbohydrate radical, and on boiling with dilute hydrochloric acid yield considerable quantities of glucosamine. The albumens and globulins contain about 10 per cent. of glucosamine. This explains perhaps the almost complete absence of carbohydrates in the egg. There is the further significant fact that the developing tissues of the embryo are very rich in mucin, a protein containing considerable quantities of glucosamine.

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[1] Bohr, "Der respiratorische Stoffwechsel des Säugethierembryos," *Skandin. Arch. f. Physiol.*, vol. x., 1900.

[2] Lochhead and Cramer, "The Glycogenic Changes in the Placenta and Fœtus of the Pregnant Rabbit," *Proc. Roy. Soc.*, Series B., vol. lxxx., 1908, p. 263.

[3] Bohr, "Über den respiratorischen Stoffwechsel beim Embryo kaltblütiger Tiere," *loc. cit.*

[4] Tangl and Farkas, "Beiträge zur Kenntniss der Ontogenese: IV. Über den Stoff u. Energieumsatz im bebrüteten Forellenei," *Pflüger's Arch.*, vol. civ., 1904.

[5] Emrys-Roberts, "A Further Note on the Nutrition of the Early Embryo with special reference to the Chick," *Proc. Roy. Soc.*, B., vol. lxxx., 1908.

[6] Hasselbalch, "Über den respiratorischen Stoffwechsel des Hühnerembryos," *Skandin. Arch. f. Physiol.*, vol. x., 1900.

[7] Mörner "Über die im Hühnereiweiss in reichlicher Menge vorkommende Mucinsubstanz," *Zeitsch. f. physiol. Chem.*, vol. xviii.

The globulin fraction of the egg-white has not yet been studied in detail. It is probable that it is a mixture of several globulins.

The investigation of the albumen fraction has been greatly facilitated by the work of Hofmeister[2] and of Hopkins,[3] which has made it possible to obtain part of the albumen fraction in a crystallised form. In this way Osborne and Campbell[4] have isolated two different albumens, the crystallisable "ovalbumen" and the non-crystallisable "conalbumen." Possibly even these two substances are mixtures of albumens, for Bondzinski and Zoja[5] claim to have isolated from the crystallisable ovalbumen several albumens by means of fractionate crystallisation. Crystalline egg albumen contains 0·13 per cent. phosphorus,[6] and is therefore another source of phosphorus in organic combination.

The white of the eggs of some Insessores has the peculiar property of forming a transparent fluorescent jelly when it is coagulated by heat.[7] The name "Tata-eggwhite" has been given to this substance. This phenomenon is probably due to the presence of a relatively large amount of basic salts in the white of the egg, since the white of a hen's egg will also coagulate to a transparent jelly if the egg has been kept for a few days in ten per cent. caustic potash.

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[1] Quoted from *Ergebnisse der Physiologie*, vol. i., Part I.

[2] Hofmeister, "Über Krystallisation des Eialbumins," *Zeitsch. f. physiol. Chem.*, vol. xiv., 1890, and vol. xvi., 1892.

[3] Hopkins and Pinkus, "Observations on the Crystallisation of Proteids," *Jour. of Physiol.*, vol. xxiii., 1898.

[4] Osborne and Campbell, *Jour. Amer. Chem. Soc.*, vol. xxii., 1900.

[5] Bondzinski and Zoja, "Über die fraktionierte Krystallisation des Eieralbumins," *Zeitsch. f. physiol. Chem.*, vol. xix., 1894.

[6] Willcock and Hardy, "Preliminary Note upon the Presence of Phosphorus in Crystalline Egg Albumen," *Proc. Cambridge Philosophical Soc.*, 1907.

[7] Tarchanoff, "Über die Verschiedenheiten des Eiereiweisses bei befiedert geborenen (Nestflüchter) und bei nakt geborenen (Nesthocker) Vögeln," *Pflüger's Arch.*, vol. xxxi., 1883. Tarchanoff, "Über Hühnereier mit durchsichtigem Eiweiss," *Pflüger's Arch.*, vol. xxxix., 1883.

Further insight into the composition of some of the proteins of the egg has been gained by means of the methods devised within recent years by E. Fischer and by Kossel, for the study of the constitution of the protein substances. By boiling with hydrochloric acid the proteins are split into the constituent amino acids and diamino acids, which are then determined as nearly quantitatively as possible.[1]

In the results given in tabular form below, the figures represent percentages, those under "total" indicating the percentage recovered in the form of amino acids and diamino acids. The absence of any one constituent is indicated by 0, the presence without quantitative estimation by +, while – indicates that investigations as to the presence or absence of a particular constituent have not been made.

		Egg Albumen (Osborne, Jones, and Leavenworth).	Vitellin (Osborne and Jones).	Keratin from Egg-Membrane (Abderhalden and Ebstein).
		Per Cent.	Per Cent.	Per Cent.
Glycine		0	0	3·9
Alanine		2·2	0·8	3·5
Valine		2·5	1·9	1·1
Leucine		10·7	9·9	7·4
Phenylalanine		5·1	2·6	–
Tyrosine		1·8	3·4	0
Serine		–	–	–
Cystine		0·4	–	7·6
Proline		3·6	4·2	4·0
Oxyproline		–	–	–
Aspartic acid		2·2	2·2	1·1
Glutamic acid		9·1	13·0	8·1
Tryptophane		+	+	–
Diamino acids	Arginine	4·9	7·5	–
	Lysine	3·8	4·8	–
	Histidine	1·7	1·9	–
Total		48·0	52·0	36·7

Of the simpler nitrogenous substances creatin and guanidin have been investigated in some detail. Creatin,[2] which contains the guanidin group in combination with acetic acid, is absent from the hen's egg. It does not appear in the developing chick until the twelfth day, when a trace is present. It then rapidly increases until the hatching period. Guanidin[3] is present in small amount in the egg—about 0·1 per cent. During the first twelve days of incubation it increases to about five times the initial value and then, after a slight fall, remains stationary during the rest of development. Guanidin is probably split off from arginine, which contains the guanidin group in combination with an amino acid.

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[1] For fuller reference see Plimmer, *The Chemical Constitution of the Proteins*, 3rd Edition, London, 1917, in the series of *Monographs on Biochemistry*; and Abderhalden, *Lehrbuch der Physiologischen Chemie*.

[2] E. Mellanby, "Creatin and Creatinin," *Jour. of Physiol.*, vol. xxxvi., 1908.

[3] Burns, "On the Precursor of Creatin in Chick Muscle," *Biochem. Jour.*, vol. x., 1916.

With regard to the question of the presence of ferments and their significance we are on very difficult ground. We must here clearly distinguish between endo-enzymes and secreted enzymes. The endo-enzymes comprise all those enzymes which are so closely bound up with the protoplasm that they can be isolated only after the cell has been destroyed. Their sphere of activity is therefore limited to the inside of the cell. Such endo-enzymes are present in every organ, and have also been found in the egg,[1] producing proteolysis and lipolysis. But since such endo-enzymes are present in many, if not in all cells, no special significance can be attached to their presence in the eggs.

The presence in the egg of secreted ferments analogous to the ferments which can be obtained by simple extraction from the digestive glands of the adult animal, would allow of more definite conclusions. The presence of such ferments has as yet not been proved with certainty, although the diastatic action of egg-yolk observed by Müller and Masuyama[2] points to the presence of a diastase analogous to the ptyalin of the saliva.

Lower Vertebrates

The covering of the eggs of the lower Vertebrates is either of the nature of a keratin, a scleroprotein rich in sulphur, similar to the membrane of birds' eggs, or it is a mucoid substance. In reptiles, like *Calotes jubatus* and *Crocodilus biporcatus*, and in Elasmobranchs, like *Raja* and *Scyllium*, the membrane is stated to consist of a keratin.[3] In the membrane of the eggs of *Tropidonotus*,[4] the British grass snake, a substance has been found which is free from sulphur and resembles the elastin which constitutes the elastic fibres of mammalian connective tissue. A similar substance is stated to occur in the egg-membrane of *Mustelus lævis*.[5] But these data are very scanty and hardly convincing. In Amphibians like the frog the membrane has been found to consist of pure mucin.[1] In Teleostean fishes it has been investigated in the case of the perch,[2] and found to be of the nature of a mucin.

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[1] Wohlgemuth, "Über das Vorkommen von Fermenten im Hühnerei," *Festschrift für Salkowski*, 1904.

[2] Müller and Masuyama, "Über ein diastatisches Ferment im Hühnerei," *Zeitsch. f. Biol.*, vol. xxxix., 1900.

[3] Krukenberg, *Vergleichende Physiologische Studien*, II. Reihe, 1 Abteilung, 1882. Neumeister, "Über die Eischalenhäute von *Echidna* und der Wirbeltiere im allgemeinen," *Zeitsch. f. Biol.*, vol. xiii., 1895.

[4] Hilger, "Ueber die Chemischen Bestandteile des Reptilieneies," *Berichte der deutschen chem. Gesellschaft*, vol. vi., 1873.

[5] Krukenberg, *loc. cit.*, 2 Abteilung, 1882.

It would be interesting to find out by systematic investigations, such as those of Pregl[3] and Buchtala,[4] whether the chemical nature of the substances protecting the egg varies with the different zoological classes, or whether there is a chemical adaptation to external environment.

The investigations of Hammarsten brought to light the interesting fact that a chemical change takes place in the cover of the eggs during ripening. The immature eggs swell with water, and a mucilaginous solution of mucus is formed, from which the mucin may be precipitated by the addition of acetic acid. If mature eggs are treated with water they do not swell. The water dissolves out the contents of the egg and the empty covers of the eggs remain, and can be transformed into mucin by weak alkali. During the ripening of the eggs there is therefore a change from mucin to mucinogen.

The composition of the eggs of fishes is essentially the same as that of birds' eggs. From the eggs of salted herrings Hugounenq has obtained the following figures calculated in percentage of the dried material:—

	Per Cent.
Pure fats - - - - -	10·35
Phosphorised fats - - - -	6·53
Keratin - - - - -	2·27
Protein ("clupeovin") - - -	81·47

The organic constituents consist chiefly of protein, fats, and phosphorised fats, with some cholesterin.

The following analysis of the ash of caviar[5] gives an idea of the composition of the ash of the eggs of fishes:—

Total ash - -	K_2O.	Na_2O.	CaO.	Fe_2O_3.	P_2O_5.	Cl.
7·70 per cent. -	3·33	30·77	5·02	0·22	10·55	47·44

In the egg the protein is present in the form of a phosphoprotein. Valenciennes and Frémy, who were the first to isolate this substance, called it Ichthulin. Later Walther showed that this substance very closely resembles the vitellin present in birds' eggs. On peptic digestion it yields an iron-containing pseudonuclein. A similar substance containing phosphorus and iron was isolated from the eggs of the salmon by Noel Paton, from cods' eggs by Levene, and from perches' eggs by Hammarsten.[1] The statement by Walther that ichthulin, on boiling with mineral acids, splits off a reducing sugar and differs in this respect from vitellin has not been confirmed by the later workers.

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[1] Giacosa. "Études sur la Composition chimique de l'Œuf et de ses Enveloppes chez la Grenouille commune," *Zeitsch. f. physiol. Chem.*, vol. vii., 1883.

[2] Hammarsten, "Chemie des Fischeies," *Skandin. Arch. f. Physiol.*, vol. xvii., 1905.

[3] Pregl, "Über die Eihäute von *Scyllium stellare* und ihre Abbauprodukte," *Zeitsch. f. physiol. Chem.*, vol. lvi., 1908.

[4] Buchtala, *ibid.*

[5] Albu and Neuberg, *Mineralstoffwechsel*, p. 241.

A protein, clupeovin, which differs in many respects from these ichthulins has been isolated from the eggs of herrings by Hugounenq,[2] and Galimard has obtained a similar substance from the eggs of frogs which he calls ranovin. Most authorities, however, doubt the chemical individuality of these proteins.

Ichthulin is probably identical with the crystalline material observed in the eggs of the tortoise, the frog, the shark, and other fishes, which is known morphologically under the name of yolk-spherules or "Dotterplättchen." The unripe eggs of the perch are embedded in a fluid from which a protein of the nature of a globulin has been isolated. This protein received the name "percaglobulin."[3] It is rich in sulphur, and is precipitated by weak hydrochloric acid. It has an astringent taste, and possesses the remarkable property of forming precipitates with some glucoproteins such as ovomucoid, and with polysaccharides such as glycogen and starch. This substance could not be found when the eggs were mature, and does not appear to be present in the ovaries of other fishes.

Very important and interesting results have been obtained by systematic chemical examinations of the muscles and ovaries of the salmon[4] and of the herring[5] at different seasons. Extensive chemical changes take place in these animals during the period of their reproductive activity. The reproductive organs develop at the expense of the muscles, which diminish in weight. This is best seen in the salmon, since this animal does not take any nourishment during its passage up the rivers. In the herring the conditions are not quite so simple, because the herring feeds until spawning occurs, although less food is taken in the later months.

In the case of the salmon, then, the ovaries are built up from material contained in the muscle. The most marked change in the muscle during that period is a loss of fat, with which the muscles are loaded when the salmon leaves the sea. The protein constituents of the muscle also diminish, but not to the same extent as the fat. There is, further, a disappearance of the inorganic phosphates of the muscle. From these substances the ovaries build up their essential constituents—the phosphoprotein ichthulin and the phosphorised fats. The source of the choline which is contained in the phosphorised fats is not yet clear. This formation by the ovaries of phosphorised fats out of fats and inorganic phosphates points to the important function which these organic phosphorus compounds have to fulfil in the developing organism (see above).

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[1] Hammarsten, "Chemie des Fischeies," *Skandin. Arch. f. Physiol.*, vol. xvii., 1905. This paper contains a detailed review of previous work done on this subject.

[2] Hugounenq, "Sur une albumine extraite des œufs des poissons," *Compt. Rend.*, vol. cxxxviii., 1904. Galimard, *ibid.*

[3] Mörner, "Percaglobulin ein charakteristischer Eiweisskörper aus dem Ovarium des Barsches," *Zeitsch. f. physiol. Chem.*, vol. xl.

[4] Miescher, *Histochemische und physiologische Arbeiten.* Noel Paton and others, "Report of Investigations on the Life-History of the Salmon in Fresh Water," *Report to the Fishery Board for Scotland*, 1898.

[5] Milroy, "Changes in the Chemical Composition of the Herring during the Reproductive Period," *Biochem. Jour.*, vol. iii., 1908, p. 366.

Not all the fat which disappears from the muscles reappears in the ovaries as phosphorised fats. A portion of it serves as a source of energy for the animal. The same applies to part of the protein of the muscle.

The iron contained in organic combination in the ichthulin of the ova is derived partly from the muscle and partly also from the blood.

Associated with the accumulation of fat in the muscles there is a storing of a lipochrome or lutein, the characteristic pink pigment of the flesh of the salmon. During its sojourn in the river this pigment disappears in part from the muscles and is transferred with the fat to the ova. This pink pigment is probably formed from another yellow pigment, which is also present in the salmon, and which is widely distributed in the animal kingdom, always closely associated with fat. It is possible that the ingestion and deposition of fat containing this yellow pigment is responsible for the formation of the pink pigment.

Invertebrates

The chemical composition of the eggs of Invertebrates does not appear to be essentially different from that of the Vertebrate eggs. The covering of the egg, which is often stated to be chitin, has been investigated by Tichomiroff[1] in the egg of *Bombyx mori*. He found it to be a protein body rich in sulphur, and similar to the keratin substances of which the membrane of the hen's egg is composed. The covering of the eggs of a cephalopod—the cuttlefish—was investigated by von Fürth.[2]

These eggs are united by their capsules, which are often coloured black by pigment, and form what are popularly known as "sea-grapes." The covering or capsule is secreted by two "nidamental glands," which open into the oviduct, and it is interesting to note that the substance secreted by these sexual glands is a mucoid substance very similar to the pseudomucin found in cysts of the human ovary (see Mammals, p. 276).

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[1] Tichomiroff, "Chemische Studien über die Entwicklung der Insekteneier," *Zeitsch. f. physiol. Chem.*, vol. ix., 1885.

[2] Von Fürth, "Über Glycoproteide niederer Tiere," *Hofmeister's Beiträge*, vol. i., 1901.

The protein substances in the eggs of Invertebrates have not been closely investigated. Vitellin is said to occur.

The eggs of insects are comparatively rich in phosphorised fats. By extraction with alcohol and ether, Dubois[1] isolated from locusts' eggs a yellowish oil containing 1·92 per cent. phosphorus.

Glycogen, purine bases, and cholesterin have been found in the eggs of *Bombyx*. The changes which take place in the chemical composition of these eggs, during incubation, have been investigated by Tichomiroff.[2]

The following table shows that a considerable amount of purine bases are formed during incubation. At the same time the fat and glycogen diminish in amount, while the cholesterin remains practically unchanged and the phosphorised fats increase slightly in amount.

		Before Incubation.	After Incubation.
		Per Cent.	Per Cent.
Purine bases		0·02	0·2
Glycogen		1·98	0·74
Present in ethereal extract	Fat	8·08	4·37
	Phosphorised fat	1·04	1·74
	Cholesterin	0·40	0·35

On the whole the changes are similar to those observed in hens' eggs, except that glycogen is present in considerable quantities in the egg and disappears during development as well as the fat, while the phosphorised fats are apparently not utilised as a source of chemical energy. The "energy of development" is very considerable, and, calculated as a percentage of the chemical energy contained in the whole egg, is as great as in the case of the developing hen's egg.[3]

Other experiments on different insects[4] have confirmed the fact that in these animals, as in birds, the main source of the energy which is used up during development is fat. No nitrogen is lost, but some of the protein material undergoes partial oxidation, to uric acid, and may thus contribute to the "energy of development." Whether the glycogen which disappears during development serves as a source of energy is doubtful. The chitin which is deposited in the cuticle of insects is a compound built up mainly of carbohydrate-groups, and it seems likely that these carbohydrate-groups are derived from the glycogen, which thus contributes to the formation of the cuticle. It is interesting to note that glycogen appears to fulfil a similar function in the developing rabbit, where it also contributes to the building up of the growing tissues.[1] It appears indeed to be a general law that carbohydrate material is essential for growth.

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[1] Dubois, "Sur l'huile d'Œufs de la Sauterelle d'Algerie (*Acridium pelerinum*)," *Compt. Rend.*, vol. cxvi., 1893.

[2] Tichomiroff, *loc. cit.*

[3] Farkas, "Über den Energieumsatz des Seidenspinners während der Entwicklung im Ei u. während der Metamorphose," *Pflüger's Arch.*, vol. xcviii., 1903.

[4] Weinland, *Zeitsch. f. Biol.*, vol. xlvii., 1905; vol. xlviii., 1907; vol. li., 1908; vol. lii., 1909. Tangl, *Pflüger's Arch.*, vol. cxxx., 1909.

Another point which emerges from these considerations of comparative biochemistry is that the synthetic capacity of the developing ovum remains constant throughout the different classes of animals which have so far been investigated. Thus in every case investigated the developing ovum has the power of synthesising the purine bases, while conversely it is unable to synthesise cholesterin, or at any rate does not require to do so, since cholesterin is always present in the egg, in amounts equal to or greater than those found in the developed embryo. Only one exception to this rule has so far been observed: in the starfish egg cholesterin is absent.[2]

The pigments have been studied especially in the eggs of Crustacea. From the eggs of *Maja squinado*, Maly[3] isolated two pigments—a red pigment, Vitellorubin, which is extremely sensitive to light, and a yellow pigment, Vitellolutein. These pigments belong to the lipochromes or luteins, which have been mentioned above. Krukenberg[4] has examined the pigments of a number of other Invertebrates. All these lipochromes have characteristic absorption spectra.

The lipochromes of *Maja* are of special interest, because a similar pigment, Tetronerythrin, has been found in the blood of *Maja* and other Crustacea. The amount present in the blood shows considerable variation. According to Heim[5] it is completely absent in the blood of the male, and appears in the blood of the female during ovulation. At this period also the ovaries, which usually have a yellowish or whitish colour, become first bright yellow and then red.

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[1] Lochhead and Cramer, *loc. cit.*

[2] Mathews, "An important Chemical Difference between the Eggs of the Sea-Urchin and those of the Starfish," *Jour. Biol. Chem.*, vol. xiv., 1913.

[3] Maly, "Über die Dotterpigmente," *Berichte der Akademie der Wissenschaften*, in Wien, vol. lxxxiii., 1881.

[4] Krukenberg, *Vergleichende physiologische Studien*, II. Reihe, 3 Abteilung, 1882, p. 6.

[5] Heim, "Sur les Pigments des Œufs des Crustacés," *Compt. Rend. Soc. Biol.*, vol. xliv., 1892, p. 467.

In Heim's[1] view this lipochrome is not formed in the ovary but in some other organ of the body, and passes at the period of ovulation into the blood, which carries it to the ovaries.

The same author, together with Abelous,[2] has proved the existence of some ferments in watery and glycerine extracts of the eggs of various Crustacea. A diastatic, a tryptic, and an inverting ferment were found. They are stated to increase in strength during the maturation of the ovum.

Heim's observations on the appearance of a lutein in the blood of the female during ovulation have acquired great significance from the remarkable work of Geoffrey Smith[3] on crustaceans. In these animals the "liver," which corresponds to almost the entire digestive and metabolic apparatus of the higher animals, varies greatly in its composition according to the condition of the crab in respect to two functions—reproduction and moulting. The quantitative variations, which are reflected also in the composition of the blood, refer to the amounts of glycogen and of fat present. In addition there are qualitative changes in the nature of the lipochrome circulating in the blood. Thus in male crabs (*Carcinus mænas*) the glycogen and fat-content of the liver is low immediately after moulting and the blood is colourless and carries little fat. In the intermediate period between two moults there is an increase in the glycogen and fat-content of the liver. The blood is pink owing to the presence of the red pigment tetronerythrin, which is deposited in the shell. The fat-content of the blood, however, remains low (0·08 per cent.).

In female crabs which are maturing their ovaries preparatory to breeding, the liver is rich in fat and contains a fair amount of glycogen. The blood is very rich in fat (0·2 per cent.). But its most striking feature is its light yellow colour, due to the presence of a yellow lutein which is being formed in the liver and carried by the blood to the ovaries, where it is deposited in the yolk of the eggs. After the eggs have been shed the blood becomes again colourless. The resulting secondary sexual characters of the male are, therefore, that the external colour is redder than that of the female, and that the male is larger.

If now crabs of both sexes are infected with Sacculina they cease to grow, moult or reproduce, but they all present the same condition, namely that of a female crab with mature ovaries, and that occurs even with male crabs. The glycogen-content is low, the fat-content high. Lutein is being formed actively in the liver, which is yellow. But the lutein does not appear in the blood, probably because the sacculina roots absorb it.

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[1] Heim, *Études sur le Sang des Crustacés*, Paris, 1892.

[2] Abelous and Heim, "Sur les Ferments des Œufs des Crustacés," *Compt. Rend. Soc. Biol.*, vol. xliii., 1891, p. 273.

[3] Geoffrey Smith, "The Effect of Reproductive Cycle on Glycogen and Fat Metabolism in Crustacea," *British Assoc.*, 1913, p. 670. See also *British Assoc.*, 1910, p. 635; 1911, p. 414.

This production in the male crab of a metabolism of the female type by infection with Sacculina may not stop merely at the appearance of female secondary sexual characters in the male, but may go so far that ova are produced in the testes.

These remarkable facts have led Doncaster[1] to assume that all individuals contain potentially the characters for both sexes—are, in fact, potential hermaphrodites. Sex is determined by an additional factor which suppresses the characters of one sex and causes those of the other sex to appear. The sex-determining factor does not introduce the characters of the corresponding sex, but merely releases them. And it does this by determining a certain type of metabolism. In other words, metabolism determines sex, not sex metabolism.

THE MALE GENERATIVE ORGANS

The Semen

The semen, *i.e.* the fluid discharged by an ejaculation, is the secretory product of the testis, epididymis, vesiculæ seminales, prostate and Littré's gland. In man it is a thick, viscous, yellowish, opalescent fluid, which after ejaculation solidifies at first and afterwards becomes fluid again. It has a peculiar smell, which becomes even more noticeable on heating. Its reaction is alkaline. Its specific gravity lies between 1·02 and 1·04. The amount discharged in an ejaculation is given differently by different authors, and probably varies with different individuals, and even with the same individual at different times. From the figures given in the literature 5 gm. may be taken to be the average amount.[2] In a normal emission of man Lode calculated that there are about 226 million spermatozoa, and that about 340,000 million must be produced in an individual between the ages of twenty-five and fifty-five.

The different classes of animals show great differences in the volume of semen ejaculated and in the relative proportion between the spermatozoa and the liquid part of the semen in which they are suspended.[3] The semen of different animals also differs in its appearance, consistency and smell. The amount of semen ejaculated by dogs varies from 0·5 to 30 or 40 c.c. This depends partly on the size of the animal but partly also on its general condition. The amount of spermatozoa present is relatively small in proportion to the liquid part of the semen. In sheep the proportion is greater but the total amount ejaculated does not exceed 2 to 5 c.c. In the horse the volume is on the average 50 to 100 c.c. but may sometimes exceed 300 c.c.

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[1] Doncaster, "The Physiology of Sex Determination," *British Assoc.*, 1913, p. 671.

[2] Acton, *Functions and Disorders of the Reproductive Organs*, 3rd Edition, London, 1862. Lode, "Untersuchungen über die Zahlen und Regenerations Verhältnisse der Spermatozoiden bei Hund und Mensch," *Pflüger's Arch.*, vol. i., 1891. Mantegazza, *Gaz. Med. Ital.*, Lombardia, 1866, quoted from Lode.

[3] Iwanoff, "Le Sperme de quelques Mammifères," *Compt. Rend. Soc. de Biol.*, vol. lxxx., 1917.

Slowtzoff[1] has made comparative analyses of the semen of man, horse, and dog, which have given the following figures:—

	Dog.	Horse.	Man.
Water	97·560	95·705	90·321
Total solids	2·450	4·295	9·679
Ash	0·687	0·915	0·901
Organic matter	1·763	3·380	8·778
All protein matter	1·259	2·238	2·854
Albumins, globulins, nucleo-proteins	0·886	1·142	2·579
Mucin	0·057	0·559	
Albumoses	0·314	0·537	0·412
Lipoids	0·182	0·172	0·208
Cholesterin	0·00075	0·0042	...
Various organic substances ("Extractives")	0·312	1·090	5·716

Human semen consists, therefore, roughly of ninety per cent. water and ten per cent. solids, which, on incineration, yield about one per cent. of ash. About one-fourth part of the solids consists of proteins, of which a nucleoprotein, traces of albumen and mucin, and an albumose-like substance have been identified. The semen of the dog and horse differs in containing more water. This difference is made up by the presence of a large amount of various organic substances in human semen, which have not been clearly identified.

In the ash of human semen, K, Na, Ca, Mg, P, Fe, and S have been found.

The quantitative analysis of the ash reveals a remarkably large amount of calcium and phosphoric acid—about twenty per cent. Ca and thirty per cent. P_2O_5. In man the amount of calcium excreted in one ejaculation is, therefore, about 0·01 gm., and exceeds that contained in an equal quantity of lime-water. Analyses of the ash of the semen of other Mammals do not appear to have been made, but it is unlikely that there are any essential differences. Since during the breeding season about fifty sheep are served by one ram, it is evident that a profound change must take place in the metabolism of phosphorus and calcium during that period. Is it not possible that the effects which are usually ascribed to a hypothetical "internal secretion" of the testis are partly due to such a direct connection with the metabolism of the body?

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[1] Slowtzoff, "Sur la Composition biochemique du Liquide spermatique," *Compt. Rend. Soc. de Biol.*, vol. lxxix., 1916. See also *Zeitsch. f. physiol. Chem.*, vol. xxxv., 1902.

The nature of the influence which the sexual glands exert upon the metabolism of the body is very complex, and has not yet been fully cleared up. Various observers have obtained very contradictory results. Since this subject will be dealt with in another chapter, we will refer to it here only in so far as it has any bearing on the calcium and phosphorus metabolism. On this point there is conclusive evidence of a morphological nature both for the male and for the female organism. Castration, if performed in youth, leads to a marked increase in the growth of the long bones. This fact, which is due to a retardation of the process of endochondral ossification taking place in these bones, accounts for the increase in stature of eunuchs and of castrated animals (see p. 323).

Similar evidence, although of a more complex character, is afforded in the case of the female by the relationship which undoubtedly exists between the ovaries and osteomalacia, a disease consisting mainly in a decalcification of the bones. It is produced probably by an abnormal function of the ovaries, since removal of the ovaries markedly improves, and sometimes cures, this condition (see p. 389). In pregnancy and parturition there is what one might call a "physiological osteomalacia" of the pelvic bones; and the activity of the mammary gland during lactation must necessarily bring about an increased calcium metabolism, since milk contains a very large amount of this element.

The organic substances in the semen may be divided into two groups. If the semen is examined microscopically it is found that it contains, on the one hand, cellular elements—viz. the spermatozoa and lymphocytes, partly in a state of degeneration; on the other hand, organic material which is partly amorphous and partly crystalline.

The amorphous material consists of:—

1. Fine albuminous granules intermixed with a few fat globules and pigmented granules.
2. Small globules of about half the size of a red blood corpuscle, consisting of a lipoid substance.
3. Oval amyloid bodies composed of concentric layers. These are, however, not invariably found.
4. The so-called "sympexions" of Robin, oval concrements of a wax-like substance, the nature of which is not known.[1]

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[1] Cohen, "Die krystallinischen Bildungen des männlichen Genitaltraktus," *Centralblatt f. allg. Pathologie u. pathol. Anatomie*, vol. x., 1899. (This paper gives a very complete bibliography.)

The crystalline substances appear only when the semen is inspissated. They present various forms—prisms, rosettes, etc., and according to Schreiner,[1] who investigated the substance very fully, these crystals are identical with those found on the surface of old anatomical preparations which have been kept in alcohol, the so-called "Böttcher's crystals." They are insoluble in alcohol, ether, and chloroform, soluble in hot water, in formol, dilute alkalis and alkali carbonates, and in dilute acids. They are coloured black by a solution of iodine in potassium iodide—"Florence's reagent" (see p. 301). Like many ammonium-bases spermine gives a characteristic colour reaction with alloxan.[2] On evaporating a solution of spermine to which a saturated solution of alloxan has been added, a red colour appears, which changes into violet on the addition of alkali. The spermine crystals are not identical, as was formerly believed, with the crystals found in the blood of leucæmic patients ("Zenker's crystals"), or with the "Charcot-Leyden crystals" which occur in the sputum of asthmatic persons.

Their chemical nature is still a matter of doubt. According to Schreiner, they are the phosphate of an organic base spermine, C_2H_5N, which Ladenburg and Abel[3] believed to be aethylenimin, C_2H_4NH. This is disputed, however, by Majert and Schmidt,[4] who ascribe to the base the formula $C_5H_{14}N_2$, and by Poehl,[5] who has attributed very remarkable properties to this substance.

According to Poehl, spermine is possessed of marked pharmacological properties, and has a powerful influence on the metabolism. It is recommended by Poehl as a valuable therapeutic agent. His statements have not been confirmed by other observers—for example Dixon[6]—and his views are now not generally accepted.

Choline, which gives the same reactions as spermine with iodine and alloxan, has also been stated to occur in the semen.

The various glands of the genital tract contribute to the formation of the semen in the following way:—

The spermatozoa are formed in the testis, which secretes an albuminous fluid as the medium in which the spermatozoa move about. Crystals smaller than the crystals of spermine-phosphate have been observed by Lubarsch[1] in the tubules of the testis. They are insoluble in formol and fifty per cent. acetic acid, and swell up under the action of alkali. Other crystalloid rod-like formations in the interstitial cells have been described by Reinke[2] and von Bardeleben.[3] The nature of these crystals, which have been found so far only in human testes, is unknown. Amyloid bodies, which are coloured blue with difficulty by iodine, have been observed by Dareste.

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[1] Schreiner, "Über eine neue organische Basis in thierischen Organismen,' *Liebig's Annalen*, vol. cxciv., 1878.

[2] Poehl, "Weitere Mitteilungen über Spermin," *Berliner klin. Wochenschrift*, 1891. See also Huntley and Wootton, *Jour. Chem. Soc.*, vol. xcix., 1911.

[3] Ladenburg and Abel, "Über das Aethylenimin," *Ber. der deutschen chem. Gesellschaft*, vol. xxi., 1888.

[4] Majert and Schmidt, "Über das Piperazin," *Ber. der deutschen chem. Gesellschaft*, vol. xxiii., 1890.

[5] Poehl, *Die Physiologisch-Chemischen Grundlagen der Spermintherapie*, St. Petersburg, 1898.

[6] Dixon, "The Composition and Action of Orchitic Extracts," *Jour. of Physiol.*, vol. xxvi., 1901.

The secretion of the epididymis has not been chemically investigated. The vesiculæ seminales secrete a substance of a protein nature[4] which in the rat and guinea-pig probably belongs to the group of histones.[5] The secretion in these animals is a white viscid fluid and has a faintly alkaline reaction.

In the guinea-pig and the rat the secretion by the vesiculæ seminales clots if brought in contact with the secretion of the glandular structure adjacent to the seminal vesicles and termed by Walker, who discovered it and has studied it in detail, the "coagulating gland." This property is perhaps a means whereby fertilisation is ensured by the formation of a clot in the outer portion of the vagina which prevents the escape of semen.

The prostate gland secretes an opaque fluid having a neutral reaction (which may become alkaline in inflammatory conditions of the prostate). It contains spermine,[6] which, when brought together with the phosphates secreted by other genital glands, forms the characteristic "Böttcher's crystals." The secretion of the prostate has the property of stimulating intensely the movements of the spermatozoa. This fact, which has been frequently confirmed,[7] has given rise to very exaggerated ideas about the mechanism of this hypothetical substance until it was found that this action is not at all specific but is given also by serum and depends simply on the CO_2 binding power of the prostatic secretion. The explanation is probably to be found in the fact observed long ago by Kölliker,[8] that the movements of spermatozoa are inactivated by acids. Now spermatozoa constantly give off CO_2 and in doing so make the fluid in which they are suspended sufficiently acid to inhibit their own movements. This self-inhibition acts as a protective mechanism. Spermatozoa are endowed with a definite store of energy, which since they are isolated cannot be replenished. Their capacity for locomotion and their length of life is therefore limited and depends on the rate with which they expend their store of energy. But whether their life be long or short, the total amount of energy which they can release as measured by the total amount of CO_2 which they excrete is constant.[1] They immobilise themselves in the testis and efferent ducts by means of their own CO_2 excretion and thus save their energy until the moment of ejaculation when the CO_2 is absorbed by the prostatic secretion.

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[1] Lubarsch, "Über das Vorkommen Krystallinischer und Krystalloider Bildungen in den Zellen des Menschlichen Hodens," *Virchow's Arch.*, vol. cxlv., 1896.

[2] Reinke, "Beiträge zur Histologie des Menschen," *Archiv f. mikroskop. Anatomie*, vol. xlvii., 1896.

[3] Bardeleben, "Beiträge zur Histologie des Hodens und zur Spermatogenese beim Menschen," *Archiv. f. Anat. u. Physiol.*, Anat. Abteilung, Supplement, 1897.

[4] Landwehr, "Über den Eiweisskörper der vesicula seminalis der Meerschweinchen," *Pflüger's Arch.*, vol. xxiii., 1880.

[5] Walker (G.), "The Nature of the Secretion of the Vesiculæ Seminales, etc.," *Johns Hopkins Hospital Bulletin*, vol. xxi., 1910.

[6] Fürbringer, "Die Störungen der Geschlechtsfunktion des Menschen"; in Nothnagel, *Pathologie u. Therapie*, vol. xix., Part III., 1895.

[7] See von Fürth, *Probleme der physiol. u. path. Chem.*, Leipzig, Vogel, p. 342, vol. i., 1912.

[8] Kölliker, "Physiologische Studien über Samenflüssigkeit," *Zeitsch. f. wissenschaftl. Zool.*, vol. vii., 1856. Gray, "Note on the Relation of Spermatozoa to Electrolytes," *Quar. Jour. Micr. Science*, vol. lxi., 1915.

The secretion of the prostate also contains the substance which gives the characteristic smell to the ejaculated semen, the lecithin-like globules, and a protein substance, which from its reactions cannot easily be classified. The statement that this protein is an albumose is probably not correct, since albumoses have never been found to occur in a living cell. Camus and Gley[2] found in the prostatic secretion of some animals a ferment, vesiculase, which has the property of coagulating the fluid in the vesiculæ seminales. The presence of this ferment in the ejaculated semen produces the formation of a coagulum. This ferment appears to have the function of ensuring fertilisation, since it occurs only in those species where the contact between male and female is of very short duration (see p. 248). Walker has shown, however (see above), that this coagulating property is not exhibited by the secretion of the prostate gland, but is found in the secretion of a separate glandular organ which he terms the coagulating gland, and which is histologically and functionally different from the prostate.

Cowper's glands secrete a stringy mucinous substance.

If a solution of iodine in potassium iodide is added to semen, brown crystals are formed (Florence's reaction). This reaction is common to many substances belonging to the group of organic ammonium bases. One of the best-known members of this group is choline, which forms part of the lecithin molecule, and is, therefore, a constituent of almost every animal cell. Probably the reaction is not due to spermine (see p. 299), as Florence[4] states, but to choline, as Bocarius[1] believes, since other secretions and tissue extracts which do not contain spermine give the same reaction.

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[1] Cohn, "Studies on the Physiology of Spermatozoa," *Biol. Bull.*, vol. xxxiv., 1918.

[2] Camus and Gley, "Action Coagulante du Liquide Prostatique sur le Contenu des Vésicules Séminales," *Compt. Rend.*, vol. cxxiii., 1896.

[4] Florence, "Du Sperme et des Taches du Sperme," *Archives d'Anthropologie Criminale*, vol. xi., 1896; vol. xii., 1897.

Joestens[2] considers that the crystals obtained in Florence's reaction are perhaps merely iodine without any choline. Warmed with a watery solution of gold tribromide semen gives on rapid cooling characteristic yellow crystals which are stated to be due to the presence of both choline and spermine and which show accordingly different forms.[3]

Another reaction for semen, which is much more specific, has been discovered by Barberio. By the addition of picric acid, fine rhombic or needle-shaped crystals are formed. It is doubtful which substance is responsible for this reaction. The observations of Littlejohn and Pirie[4] show that the substance which forms the crystalline picrate is secreted by the prostate and by Cowper's glands, and, further, that this substance appears to be specific for human semen, since a negative result is obtained with the semen of monkeys, rabbits, and rats.

THE CHEMISTRY OF THE SPERMATOZOÖN[5]

Owing to the brilliant work of Miescher,[6] which has been continued by Kossel[7] and his pupils, our knowledge of the chemistry of the spermatozoön is more complete than that of any other cell.

Thanks to the intelligent generosity of the head of a large fishery concern in Bâle, Miescher obtained a liberal supply of the milt of the salmon, the sexual organs of which develop during the passage up the Rhine. By controlling his mechanical manipulations by means of histological observations Miescher was able to investigate separately the different morphological elements of the spermatozoa. The tails of the spermatozoa are very rich in phosphorised fats, and contain besides a typical protein, cholesterin, and fat, in the following proportions:—

	Per Cent.
Proteins	41·90
Phosphorised fats	31·83
Cholesterin, fats	26·27

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[1] Bocarius, "Zur Kenntniss der Substanz welche die Bildung von Florenceschen Krystallen bedingt," *Zeitsch. f. physiol. Chem.*, vol. xxxiv., 1902.

[2] Joestens, "Experimentelle Untersuchungen über die Florence'sche Reaktion," *Vierteljahrschrift f. gerichtliche Medizin*, vol. xlv., 1913.

[3] De Dominicis, "Über eine Spermareaktion mit Goldtribromür," "*Vierteljahrsch. f. gerichtliche Medizin*, vol. xliv., 1912.

[4] Littlejohn and Pirie, "The Micro-Chemical Tests for Semen," *Edin. Med. Jour.*, 1908. (This paper contains references to the literature.)

[5] For a detailed account of this subject and the literature see Burrian, "Chemie der Spermatozoen," I., in *Ergebnisse der Physiologie*, vol. iii., 1904; and "Chemie der Spermatozoen," II., in *Ergebnisse der Physiologie*, vol. v., 1906.

[6] Miescher, *Histochemische und Physiologische Arbeiten. Gesammelt und Herausgegeben von Seinen Freunden*, vol. ii., Leipzig, 1897.

[7] Kossel, "Über die einfachsten Eiweisskörper," *Biochemisches Centralblatt*, vol. v., Part I., 1906-07.

Similar conditions were found to exist in the case of other fishes and in the case of the ox. The heads were found to contain only traces of fat, lecithin and cholesterin, and to be composed almost entirely of a substance very rich in phosphorus. This on further investigation proved to be a combination of a basic substance, very rich in nitrogen, which Miescher called protamine, and a substance rich in phosphorus, having the nature of an acid and belonging to the group of substances known as nucleinic acids, which occur in the nuclei of somatic cells in combination with protein substances as the so-called nucleoproteins.

The comparative chemical investigations of Kossel proved that, while the nucleinic acid radical present in the spermatozoa of various species of fishes shows only very little variation, the basic part is different for each species. It has, therefore, been found convenient to distinguish these basic substances by separate names, derived from the Latin names of the species of the fish in which they occur. The basic substance of the head of the spermatozoön of the salmon is salmine, that of the herring clupeine, and so on. Since they have certain general chemical and physical characters in common they have been classed together in a group, which has received the name "Protamine," which was originally used by Miescher to denote the basic substance in the spermatozoa of the salmon.

The protamines are strongly basic substances which absorb carbonic acid from the air. They are soluble in water, insoluble in alcohol and ether; not coagulable by heat; free from sulphur. They are very rich in nitrogen, the percentage amount varying from 33 per cent. to 25 per cent., while that of an albumen or globulin is about 16 per cent. They give a strong biuret reaction. Like other proteins, they are precipitated by tannic acid, phosphotungstic acid, picric acid, and ferrocyanic acid; but while the proteins are precipitated by these reagents in acid solution only, the protamines, by virtue of their basic character, form a precipitate with these reagents even in alkaline solution. They form compounds with the salts of the heavy metals (copper, mercury, silver, platinum). The protamines combine with many other protein substances in neutral or faintly alkaline solution, so that a precipitate is formed if, for example, a solution of protamine is added to a solution of caseinogen.[1]

If injected into an animal they have a strongly toxic action, even if small doses are given.[2]

Although differing in many respects from the protein substances, the protamines have been shown by Kossel to have a constitution so similar to that of the proteins that they are now considered to represent one group of the protein substances.

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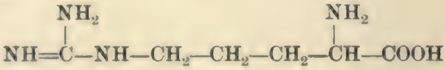
[1] Hunter (A.), "Über die Verbindungen der Protamine mit anderen Eiweisskörpern," *Zeitsch. f. physiol. Chem.*, vol. liii., 1907.

[2] Thompson, "Die physiologische Wirkung der Protamine," *Zeitsch. f. physiol. Chem.*, vol. xxix., 1899.

The study of the products of hydrolytic decomposition shows that while in the case of the typical proteins, such as the proteins of muscle, of milk, or of the serum, the nitrogen is bound up in the form of a great many different substances, *e.g.* tyrosine, leucine, alanine, glycine, cystine, etc., of which as many as fifteen have been isolated, the protamine molecule is composed of only a few constituent substances. And further, while in the case of the typical proteins the main bulk of the substance obtained on hydrolysis belongs to the monoamino acids, the protamines are composed largely of the diamino acids; arginine, lysine, and histidine, which, from their basic nature and the fact that they contain six carbon atoms, have received the name "hexone-bases."

Of these the most important one is arginine, which, on boiling with baryta, is decomposed into urea and diaminovalerianic acid (ornithin), and has the structure—



$$NH{=}\overset{NH_2}{\overset{|}{C}}{-}NH{-}CH_2{-}CH_2{-}CH_2{-}\overset{NH_2}{\overset{|}{C}}H{-}COOH$$

In salmine, for instance, eight-ninths of the nitrogen is bound up as arginine, while the remainder of the nitrogen is present in the form of monoamino acids, viz. serine, monoaminovalerianic acid and proline, in the following proportions: 10 molecules of arginine + 2 molecules of serine + 2 molecules of proline + 1 molecule of aminovalerianic acid. Similar relations are found to exist in the case of scombrine and clupeine. In both these protamines eight-ninths of the total nitrogen is present in the form of arginine, which is combined with alanine and proline in the case of scombrine, and with alanine, proline, serine, and aminovalerianic acid in the case of clupeine.

Since eight-ninths of the nitrogen of these three protamines is present in the form of arginine, and since arginine contains four nitrogen atoms, while the amino acids with which it is combined contain only one nitrogen atom, it follows that in these three protamines the number of arginine molecules must be twice as great as the total number of monoamino acid molecules present in the protamine molecule.

The investigations of Kossel and Pringle[1] have shown that substances can be obtained by partial hydrolysis of these protamines, the so-called "protones," which represent intermediate decomposition products between these protamines and the amino acid units of which the protamines are built up, and that these protones again contain eight-ninths of their total nitrogen in the form of arginine. It follows, then, that the molecules of salmine, scombrine, and clupeine have a symmetrical structure, and are built up of molecular complexes containing always twice as many arginine molecules as monoamino acid molecules.

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[1] Kossel and Pringle, "Über Protamine und Histone," *Zeitsch. f. physiol. Chem.*, vol. xlix., 1906.

In other protamines the amount of arginine is smaller, while lysine is found to be present. At the same time the number of monoamino acids bound up in the protamine molecule increases, so that the different protamines exhibit varying degrees of complexity. Ammonia and certain monoamino acids (glycocoll, phenylalanine, glutaminic acid, aspartic acid, the sulphur-containing cystine) are never present.

In some fishes—*e.g.* *Gadus morrhua*,[1] *Lota vulgaris*[2]—the basic substances isolated from the spermatozoa differ essentially from the protamines, and resemble in character more the typical proteins. Their nitrogen content varies between 16 per cent. and 18 per cent. On hydrolysis the yield of diamino acids is very much smaller than in the case of the protamines. Only 30 to 40 per cent. of diamino acids, among which arginine again preponderates, are obtained. Accordingly they are not so strongly basic as the protamines. They contain cystine. They are precipitated by ammonia, a reaction which the protamines do not give. They resemble in their behaviour substances which have been isolated from the nuclei of somatic cells, *e.g.* the blood corpuscles of the fowl, the thymus, etc., and which form another class of the protein substances, to which the name *histone* has been given. In their properties and their composition these substances, therefore, take a place between the typical proteins and the protamines.

The substance isolated from the spermatozoa of the carp, cyprinine (or rather the two cyprinines, since two slightly different substances have been isolated), is on the border-line between the protamines and the histones. The cyprinines do not contain any cystine, they are not precipitated by ammonia, and only about thirty-five per cent. of their total nitrogen is present in the form of diamino acids, mainly as lysine in the one of the two cyprinines.[3]

The chemical differences which exist between the spermatozoa of the different species and orders occur arbitrarily without reference to zoological relationship.

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[1] Kossel and Kutscher, "Beiträge zur Kenntniss der Eiweisskörper," *Zeitsch. f. physiol. Chem.*, vol. xxxi., 1900.

[2] Ehrström, "Über ein neues Histon aus Fischsperma," *Zeitsch. f. physiol. Chem.*, vol. xxxii.. 1901.

[3] Kossel and Dakin, "Beitrag zum System der einfachsten Eiweisskörper," *Zeitsch. f. physiol. Chem.*, vol. xl., 1904.

The significance of the presence of histones in the spermatozoa of some fishes becomes more apparent if the development of the sexual organs is considered.

It was Miescher who pointed out that in the salmon the sexual organs develop at the expense of the muscular system and that the salmine deposited in the testis during the breeding season must be derived from the proteins of the muscle, since the fish does not take any food during that period. A comparison between the amount of arginine present in salmine and that present in the muscle of the salmon, shows[1] that all the arginine deposited as salmine during the breeding season can be accounted for by the arginine which becomes available by the involution of the muscular elements.

This result would suggest that the formation of salmine is not due to a profound chemical alteration of the various constituents of the muscle-proteins, transforming the divers substances into arginine, but rather to a gradual enrichment in arginine of the muscle-protein by the splitting off of a number of the other constituent substances.

The investigation of the unripe spermatozoa of the salmon[2] and of the mackerel[3] has shown indeed that instead of a protamine a histone is present, *i.e.* a substance which represents the transition stage between the typical proteins and the protamines.

It would appear, therefore, that in the fishes the chemical processes which lead to the formation of the spermatozoa consist of a rearrangement of the constituents of the proteins of somatic tissue, so that a gradual accumulation of the basic substances rich in nitrogen takes place. This change leads at first to the formation of histones, and in some species stops here. In the majority of cases the change proceeds to the formation of substances belonging to the protamines.

In some Invertebrates (*Arbacia pustulosa*,[4] *Sphærechinus granularis*[5]) the spermatozoa have been investigated and histones have been found to be present.

Of the higher Vertebrates, the spermatozoa of the frog, the cock, the boar, and the bull have been examined,[1] but neither protamines nor histones were found.

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[1] Kossel, "Einige Bemerkungen über die Bildung der Protamine im Thierkorper," *Zeitsch. f. physiol. Chem.*, vol. xliv., 1905. Weiss, "Untersuchungen über die Bildung des Lachs-Protamins," *Zeitsch. f. physiol. Chem.*, vol. lii., 1907.

[2] Miescher, "Physiologisch-Chemische Untersuchungen über die Lachsmilch," *Histochemische Arbeiten*, *Archiv f. Experimentelle Pathologie u. Pharmakologie*, vol. xxxvii., 1896-97.

[3] Bang (I.), "Studien über Histon," *Zeitsch. f. physiol. Chem.*, vol. xxvii., 1899.

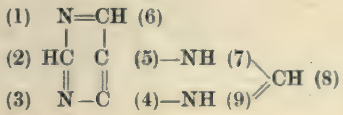
[4] Mathews, "Zur Chemie der Spermatozoen," *Zeitsch. f. physiol. Chem.*, vol. xxiii., 1897.

[5] Kossel, "Über die einfachsten Eiweisskörper," *Biochemisches Centralblatt*, vol. v., 1906-07.

The acid substance isolated from the spermatozoa, the nucleic acid, does not show any variation in the different species and classes of animals. It is, in fact, so similar to the nucleic acid present in the nuclei of somatic cells, that it is now considered to be identical with the nucleic acid prepared from the thymus, which has been studied in great detail. These nucleic acids do not belong to the proteins, but they exist in the cell always in combination with proteins as nucleins or as nucleoproteins, according to the amount of protein present in the combination.

The nucleic acids are dry, pulverulent, white substances of a decidedly acid character, containing nine to ten per cent. of phosphorus, not easily soluble in cold water, but readily dissolved by alkalis or ammonia. They are precipitated from their solutions by mineral acids and by alcohol. They form insoluble salts with the heavy metals and with barium, calcium, and strontium. If pure, they do not give the colour reactions for proteins. They rotate polarised light to the right. A solution of nucleic acid, acidified with acetic acid, gives a precipitate with protein solutions. By boiling the watery solutions the nucleic acids are partially decomposed.[2] Complete hydrolysis is brought about by treatment with hot acids. The main products of hydrolysis which have been thus obtained from various nucleinic acids can be grouped under five headings :—

1. Phosphoric acid.
2. Lævulinic acid, a substance formed by the oxidation of carbohydrates, and indicating the presence of a hexose (the nucleic acids from plants, yeast for instance, contain a pentose).
3. Derivatives of purine—



namely—

Adenine = 6-Aminopurine ; Hypoxanthine = 6-Oxypurine ;
Guanine = 2 Amino-6 Oxypurine ; Xanthine = 2-6 Dioxypurine.

Of these only adenine and guanine are present as such in the nucleic acid molecule, while hypoxanthine and xanthine are formed from them in the process of hydrolysis by a secondary reaction.

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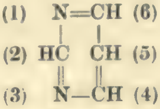
[1] Miescher, *loc. cit.*, "Die Spermatozoen einiger Wirbelthiere," *Histochemische Arbeiten* ; Mathews, *loc. cit.*

[2] For a complete account of the chemistry of nucleic acid see Jones, "Nucleic Acids," in the series *Monographs on Biochemistry*, 2nd Edition, London, 1920.

4. Derivatives of pyrimidine—



namely—

Cytosine = 6 Amino-2 Oxypyrimidine;
Uracil = 2-6-Dioxypyrimidine;
Thymine = 5 Methyl-2-6 Dioxypyrimidine (Methyl-Uracil).

Of these cytosine and thymine are present as such in the nucleic acids obtained from animals, while uracil is formed from cytosine by a secondary reaction in the process of the splitting up of the nucleic acid.

In the nucleic acids of plant origin uracil is bound up as such and takes the place of thymine. So far as our present knowledge goes only two nucleic acids—or groups of nucleic acids—occur in nature; one obtainable from the nuclei of animal cells, the other from the nuclei of plant cells. The difference consists, as has just been stated, in the presence of a hexose and of thymine in the animal nucleic acid, while the plant nucleic acid contains in their stead a pentose and uracil. It is, however, significant that the only two exceptions have so far been found in certain nucleic acids obtained from the generative organs. The nucleic acid obtained from the eggs of a fish (*Gadus aiglefinus*) contains uracil and a pentose but no thymine and no hexose.[1] And while nucleic acid prepared from ripe spermatozoa does not contain pentoses, these substances are stated to be present in the nucleic acid of the testis of the bull,[2] which represents the acid constituent of the nuclei of the sexual element in the various stages of their development. Since the statement of the presence of a pentose in the nucleic acid from the testis of the bull is based only on the preparation of an osazone, further investigation on this point and analytical data are necessary before it can be accepted.

The origin of the purine and pyrimidine derivatives which form part of the nucleic acid molecule is as yet obscure. In experiments on the developing ovum it has been shown (see p. 282) that the living cell has the power of synthesising these substances.

This has been confirmed by experiments on Mammals by various observers.[1] The nature of the substances which supply the material for the formation of the purine bodies remained unknown until Ackroyd and Hopkins[2] found that in the urine of rats the amount of allantoin, which is derived from uric acid, was greatly diminished when the diet of these animals was so constituted as to be free from the diamino acids histidine and arginine. They conclude, therefore, that these constituents of the protein molecule represent specifically the raw material for the synthesis of the purine bodies.

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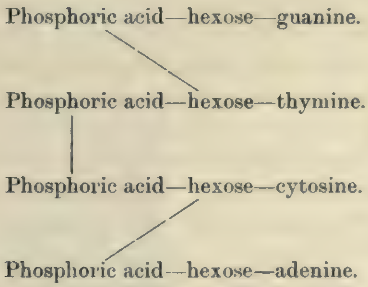
[1] Levene and Mandel, "Über die Nukleinkörper des Eies des Schellfisches (*Gadus æglefinus*)," *Zeitsch. f. physiol. Chem.*, vol. xlix., 1906.

[2] Steudel, "Über die Kohlenhydratgruppe in der Nukleinsäure," *Zeitsch. f. physiol. Chem.*, vol. lvi., 1908.

The structure of nucleic acid is almost completely established. As has been stated above, animal nucleic acid contains phosphoric acid, a hexose and four nitrogenous ring compounds. These are arranged in such a way in the nucleic acid molecule that a carbohydrate group links a phosphoric acid group with either a purine or a pyrimidine group. Such a compound is called a *nucleotide*. As an example, guanine-nucleotide may be given thus: phosphoric acid—hexose—guanine. In nucleic acid four such mononucleotides are bound together, so that the structure of animal nucleic acid may be represented thus:—



Phosphoric acid—hexose—guanine.
Phosphoric acid—hexose—thymine.
Phosphoric acid—hexose—cytosine.
Phosphoric acid—hexose—adenine.

In other words, the "skeleton" of the nucleic acid molecule is formed by four molecules of phosphoric acid combined with four molecules of a sugar:[3] a tetraglyco-phosphoric acid, similar to the glycerophosphoric acid which forms the "skeleton" of phosphorised fats. In the nucleic acid molecule this glycophosphoric acid is combined with four different nitrogenous substances, of which two are pyrimidine derivatives and two are purine derivatives.

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[1] Burian and Schur, "Über Nukleinbildung im Säugethierorganismus," *Zeitsch. f. physiol. Chem.*, vol. xxiii., 1897. Osborne and Mendel, "Beobachtungen über Wachstum bei Fütterungsversuchen mit isolierten Nahrungssubstanzen," *Zeitsch. f. physiol. Chem.*, vol. lxxx., 1912. Benedict, "Uric Acid in its Relation to Metabolism," *Jour. Lab. and Clin. Medicine*, vol. ii., 1916.

[2] Ackroyd and Hopkins, "Feeding Experiments with Deficiencies in the Amino-Acid Supply: Histidine and Arginine as possible Precursors of Purines," *Biochem. Jour.*, vol. x., 1916.

[3] The sodium-salt of a tetraphosphoric acid can be prepared by fusing together the sodium metaphosphate and pyrophosphate (Kraut and Uelsmann, *Liebig's Annalen*, vol. cxviii., 1861). The organic derivatives of this base have not yet been studied.

Reference has already been made to the fact that in the salmon the material for the growth of the testis is supplied by the muscle undergoing atrophy. The analogy existing between the glycophosphoric acid which forms the "skeleton" of the nucleic acid, and the glycerophosphoric acid which forms the skeleton of phosphorised fats, suggests that the glycerophosphoric acid present in the muscle as phosphorised fat furnishes the material from which the glycophosphoric acid bound up in the testis as the nucleic acid is formed. This view is supported by the fact that, during the period of the growth of the testis, the blood of the salmon is exceptionally rich in phosphorised fats, and that the tail of the spermatozoön is also very rich in phosphorised fats. It would appear that these substances, after having been transported to the testis, are there built up partly into the nucleus of the spermatozoön, while part remains accumulated in the tail of the spermatozoön as reserve material.

Owing to their characteristic histochemical reactions the fate of the lipoids in the testis can be followed to a certain extent. In the active adult testis the interstitial cells are loaded with globules of lipoid material. It is double-refracting in addition to staining with Sudan. and with osmic acid after bichromate, and is therefore not ordinary neutral fat, but a mixture of ordinary fat with lipoids, such as lecithin and cholesterin, similar to the mixture which is present in the adrenal cortex or the corpus luteum. Similar globules are present also in small amounts in the seminiferous tubules, where they show a regular distribution in the spermatogonia, and more especially in the Sertoli cells,[1] to which the spermatids are attached while undergoing differentiation into spermatozoa and from which they presumably absorb the lipoids. From observations on human material Mott[2] has drawn the significant conclusion that the interstitial cells are free from lipoids until puberty, when active spermatogenesis begins. The importance of a normal metabolism of lipoids is further demonstrated by the correlation which exists between abnormalities in the adrenal cortex and the function of the testis. Hypertrophy of the adrenal cortex is associated with sexual precocity. Conversely Mott has found in cases of dementia præcox an atrophic adrenal cortex poor in lipoids and associated with it regressive atrophy of the testis. The writer[3] has found a similar correlation in the condition produced by feeding animals on a diet free from vitamins. This leads to disturbances in the distribution of the cortical lipoid of the adrenal and there is also atrophy of the seminiferous tubules of the testis.

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[1] Schafer, *Text-book of Microscopic Anatomy*, Longmans, Green & Co., 1912, p. 622.

[2] Mott, "Normal and Morbid Conditions of the Testes from Birth to Old Age in one hundred Hospital and Asylum Cases," *Brit. Med. Jour.*, 1919.

[3] Cramer, Unpublished observations.

The observations of Miescher[1] allowed of a quantitative estimation of the amount of nucleic acid and protamine present in the head of the spermatozoa of the salmon after the fat had been removed. 60·5 per cent. of nucleic acid was found to be combined with 35·5 per cent. of salmine, so that 96 per cent. of the head of the spermatozoön consists of protamine nucleate. This protamine nucleate is, however, not of the same nature in different parts of the head, the outer layer containing a basic nucleate rich in protamine, while the inner portion is composed of an acid nucleate poorer in protamine.

The same quantitative relations have been shown to exist in the spermatozoa of the herring,[2] and similar conditions may be assumed to exist in the case of the spermatozoa of other animals, the only difference being the nature of the protein molecule which is combined with the nucleic acid. It is a protamine or a histone in the case of the fishes, but a typical protein in the case of the higher Vertebrates.[3]

Of the remaining four per cent. about one-half consists of inorganic salts, mainly calcium phosphate and calcium carbonate, while the other half consists of an organic substance, the composition of which has not yet been recognised. The most important fact known about it is that it contains 0·12 per cent. iron in organic combination. The presence of iron can be recognised only after incineration. To this iron-containing organic substance Burrian[4] applies the name "Karyogen," a word originally coined by Miescher to designate the residue which he obtained after what Schmiedeberg's[5] calculations showed to be an incomplete extraction of the protamine and nucleic acid from the heads of the spermatozoa of the salmon. Since Macallum[6] was able to demonstrate by means of a microchemical method the presence of iron in the chromatin of the nuclei of cells, it seems possible that the "Karyogen" represents the chromatin substance of the spermatozoön.

The chemical analysis of the spermatozoön is therefore complete. It shows that the tail is very rich in phosphorised fats which are accompanied by cholesterin, fats, and a typical protein. The head consists almost entirely (ninety-six per cent.) of a substance—a nucleoprotein—one component of which is constant for the different species and classes—the nucleic acid. The other more or less basic component varies widely for the different classes of Vertebrates, and shows minor variations for the different species in any one class. Besides this nucleoprotein, another organic substance, containing iron in organic combination, is present in very small amounts.

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[1] Miescher, *Histochemische Arbeiten.*

[2] Bendix and Elstein, "Über den Pentosengehalt tierischer und menschlicher Organe," *Zeitsch. f. allgem. Physiologie*, vol. ii., 1902.

[3] Mathews, "Zur Chemie der Spermatozoen," *Zeitsch. f. physiol. Chem.*, vol. xxiii., 1897.

[4] Burrian, *Ergebnisse der Physiologie*, vol. v., 1906.

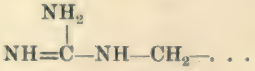
[5] Miescher, "Physiologisch-chemische Untersuchungen über die Lachsmilch, nach den hinterlassenen Aufzeichnungen u. Versuchsprotokollen des Autors bearbeitet u. herausgegeben von O. Schmiedeberg," *Arch. f. experimentelle Pathologie u. Pharmakologie*, vol. xxxvii., 1896, and in *Histochemische u. Physiologische Arbeiten von Miescher.*

[6] Macallum, "On the Demonstration of the Presence of Iron in Chromatin by Microchemical Methods," *Proc. Roy. Soc.*, vol. l., 1892.

It is perhaps natural that attempts should have been made to associate these different substances with the functions of the spermatozoön. But such speculations are hardly justifiable until our knowledge of the nucleus of the ovum is as complete as it is in the cases of the male nucleus. At present we know practically nothing of the chemical composition of the nucleus of the ovum. Nor is it likely—and Miescher himself clearly recognised this—that the intricate processes which are connected with fertilisation and heredity are directly dependent upon such crude chemical facts as the percentage of arginine or serine, or the composition of nucleic acid.

We are on safer ground when we consider the head of the spermatozoön simply as a typical nucleus, and when we draw deductions from the chemical composition of the nuclear material of the spermatozoön, as to the functions of the nucleus generally.

It is a very suggestive fact that the nucleus—that is to say, that part of the cell which is pre-eminently concerned in the new formation of living material—is distinguished by the presence of pyrimidine and purine derivatives, substances rich in nitrogen, which are arranged in a chain of alternating C and N atoms.[1] In the spermatozoön, where the nuclear function finds its most pronounced expression, we find, at least in the case of the fishes, a further concentration of such groups with alternating C and N atoms. For, besides the pyrimidine and purine derivatives of the nucleic acid part, there is also present the basic protamine part. As has been explained above, this part is composed largely of arginine, which, as the formula given on p. 304 shows, contains the group—



$$NH{=}\overset{\overset{\displaystyle NH_2}{|}}{C}{-}NH{-}CH_2{-}\ldots$$

These facts suggest that this special arrangement of alternating C and N atoms is the chemical expression of the specific function of the nucleus, and that this arrangement plays a special part in bringing about the chemical processes which lead to growth and to the new formation of living matter.

In the case of the other organic compound present in every nucleus, which contains iron in organic combination, the evidence that it plays an active part in the synthetic functions of the nucleus is even more suggestive. It was shown by Spitzer[1] that the oxidising enzymes which are present in every cell are localised in the iron-containing constituent of the nucleus, and Loeb concludes that the nucleus must be regarded as the essential respiratory or oxidising organ of the cell.[2] Oxidation processes are generally supposed to be necessary only for the transformation of chemical energy into heat and mechanical work. But they are, according to Loeb, equally necessary for other more important and more general vital processes, *i.e.* growth and cell division, which come to a standstill in the absence of oxygen. As a rule, cell division follows upon the synthesis of nuclear material, especially chromatin material, from the protoplasm of the cell. If we accept Schmiedeberg's[3] view that in the living cell synthetic processes occur through the intervention of oxygen, we may conclude that the oxygen which is required for the process of cell division is needed for the synthesis of nuclear material, and, since it is the iron-containing organic compound present in the nucleus which has the power of bringing about oxidations, it would follow that the synthetic functions of the nucleus (and hence cell division) are dependent upon this compound. It must, however, be understood that these considerations are still very hypothetical, and that other biologists[4] deny that the nucleus is the respiratory or oxidising centre of the cell.

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[1] Kossel, "Einige Bemerkungen über die Bildung der Protamine im Thierkörper," *Zeitsch. f. physiol. Chem.*, vol. xliv., 1905.

Similar observations on the localisation of the intracellular oxidising processes in the nucleus have been made by Lillie[5] and by Unna.[6]

THE BIOCHEMISTRY OF FERTILISATION: ARTIFICIAL PARTHENOGENESIS

What is the biochemical significance of the process of fertilisation? The answer to that question we owe mainly to the brilliant work of Jacques Loeb[7] on artifical parthenogenesis. In 1899 he found,[8] as the result of systematic attempts to induce development in the unfertilised eggs of a sea-urchin (*Arbacia*), that such eggs, when exposed for two hours to a mixture of equal parts of sea-water and of a 10/8 m. $MgCl_2$ solution and then replaced in normal sea-water, developed into swimming larvæ. The effect of adding the $MgCl_2$ solution was to raise the osmotic pressure considerably, and further experiments showed that this increase of osmotic pressure was the essential factor in this original method of artificial parthenogenesis. It had thus become possible to replace the mysterious complex "living spermatozoön" by well-known physico-chemical agencies. He found subsequently that a great variety of different agencies are able to induce parthenogenesis. From a wealth of experimental data Loeb has evolved a theory which may be summarised as follows: The development of the mature ovum is dependent upon two processes. It is initiated by a cytolysis affecting the periphery of the cell. Morphologically this process is represented by the formation of a fertilisation membrane, which is really the essential step in the activation of development. Membrane formation can be induced by any agent having a cytolytic action: fatty acids, saponin and similar substances, lipoid solvents, bases, rise in temperature, certain inorganic salts, *e.g.* $BaCl_2$, $CaCl_2$, KCNS, and lastly, the blood-serum or cell extracts of certain species, but foreign to the species to which the ovum belongs.

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[1] Spitzer, "Die Bedeutung gewisser Nukleoproteide für die oxydative Leistung der Zelle," *Pflüger's Arch.*, vol. lxvii., 1897.

[2] Loeb, *Dynamics of Living Matter*, New York, 1906.

[3] Schmiedeberg, "Über Oxydationen und Synthesen im Thierkörper," *Archiv f. experimentelle Pathologie u. Pharmakologie*, vol. xiv., 1881.

[4] See Verworn, *Allgemeine Physiologie*, 1909; also Pighini, "Über die Indophenyloxydase im Nervensystem," *Biochem. Zeitsch.*, vol. xlii., 1912.

[5] Lillie (F.), "On the Oxidative Properties of the Cell Nucleus," *Amer. Jour. of Physiol.*, vol. vii., 1902.

[6] Unna and Golodetz, "Biochemie der Haut," in Oppenheimer's *Handbuch der Biochemie*, Erganzungsband, Jena, Gustav Fischer, 1913.

[7] Loeb (Jacques), *Artificial Parthenogenesis and Fertilisation*, University of Chicago Press, Chicago, 1913.

[8] Loeb (J.), "On the Artificial Production of Normal Larvæ from the Unfertilised Eggs of the Sea-Urchin," *Amer. Jour. of Physiol.*, vol. iii., 1900.

The next question is: Why is a cytolysis necessary to initiate the development of the egg? The answer is to be found in the observations of Warburg,[1] that the oxygen consumption of the sea-urchin egg shows a sudden increase after fertilisation to seven times that of the unfertilised egg. Mechanical disintegration of the unfertilised egg, even injury to the cortical layer, results in a similar increase in oxygen consumption. These results were confirmed by Loeb and Wasteneys for the eggs of *Strongylocentrotus purpuratus*. They also found an increased oxygen consumption after the action of cytolytic agents and after the formation of a fertilisation membrane. It would follow that the contents of the unfertilised egg are in a highly oxidisable condition, but that the cortical layer of such an egg does not present conditions favourable for the oxidation of its contents to take place. Cytolysis removes an obstacle so that the oxidations become possible. Loeb suggests that by breaking down the peripheral lipoid emulsion, certain substances which were previously solid are liquefied and allowed to diffuse into the egg, where they start or accelerate the chemical processes underlying development. The oxygen consumption increases before cell division sets in, and oxygen consumption and development are to a large extent independent of each other. Development is therefore not the cause of the increased oxygen consumption. On the contrary, the increased oxygen consumption is the cause of development, and fertilisation is the method by which this increased oxygen consumption is induced. This conception has received strong confirmation by the recent work of Shearer.[1] On bringing together the eggs and the sperm of *Echinus microtuberculatus* there is at once during the first minute an enormous increase in the oxygen consumption. In fact, this increase during the first minute is much greater than that observed at any subsequent period. The significant fact is that this increase occurs before the spermatozoa have penetrated the cell membrane. The increased oxygen consumption must therefore be due to a change at the extreme periphery of the egg. Shearer suggests that the cortical lipoid layer contains traces of iron. As we have seen (see p. 313) traces of iron may act as a catalyst: for instance, they greatly increase the oxygen absorption by emulsions of lecithin.[2] In the unfertilised egg the iron is present in the cortical layer in an inactive condition, and is set free by the alteration in the cortical layer induced by the spermatozoön.

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[1] Warburg, "Beiträge zur Physiologie der Zelle, insbesondere über die Oxydationsgeschwindigkeit in Zellen," *Ergebnisse der Physiologie*, 1914, vol. xiv.; see also *Zeitsch. f. physiol. Chem.*, vol. lvii., 1908; vol. lx., 1909; vol. lxvi., 1910.

If the initial cytolysis is allowed to proceed unchecked the eggs, although they begin to divide, eventually undergo complete cytolysis and die. A second corrective process is necessary to save the life of the cell. Experimentally this second corrective life-saving process consists either in stopping oxidation altogether by immersing the eggs in a potassium cyanide solution or by depriving them of oxygen, or by placing the eggs for a short time in a hypertonic salt solution containing oxygen. The eggs then develop in the same way as if they had been fertilised by a spermatozoön. They develop into larvæ, and such larvæ can, with the necessary care, be reared to sexual maturity. Delage has succeeded in doing so in the case of the sea-urchin. Loeb and Bancroft raised a parthenogenetic frog through metamorphosis and found that its sex glands contained eggs.

How this second process, which Loeb terms the "corrective factor," operates is not very clear. One can only conclude that it is not only necessary that the metabolism of the mature ovum should be stimulated and reach a certain optimum, but the processes thus initiated by the formation of a fertilisation membrane must be properly co-ordinated. Otherwise the entire developmental process may go astray.

If it be admitted that artificial parthenogenesis reproduces the

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[1] Shearer, "On the Oxidation Processes of the Echinoderm Egg during Fertilisation," *Proc. Roy. Soc.*, B., vol. xciii., 1921. See above, pp. 186-197.

[2] Thunberg, *loc. cit.* See also Warburg and Meyerhof, *Zeitsch. f. physiol. Chem.*, 1913, vol. lxxxv.

conditions governing fertilisation by a spermatozoön, then it follows that a spermatozoön should contain two substances, namely, a cytolysin and a substance inhibiting the initial cytolysis. The presence in the spermatozoön of a cytolysin can indeed be proved. Extracts of the testis of a cock, or the dead semen (killed by heating) of a starfish or a mollusc, will induce the initial process of cytolysis in the eggs of a sea-urchin. The dead semen of a sea-urchin, however, is quite inactive against the eggs of a sea-urchin. The observations of Pieri,[1] of Dubois,[2] and of Winkler,[3] who claimed to have extracted from the spermatozoa of various invertebrates ferments which induced segmentation of the mature ovum of the same species, were proved to be due to fallacies by Gies[4] and by Cremer.[5] The fact is, as Loeb showed, that the extracts must be prepared from the spermatozoa belonging to a foreign species. This apparently paradoxical phenomenon is in agreement with our knowledge of the actions of cytolysins generally. The cytolysins present normally in the serum or the cells of one animal are always inactive against the cells of animals of the same species, and act only against cells of animals of a different species. The explanation of this fact is to be found, according to Loeb, in the diminished permeability of the cells of one species towards the cytolysins produced by the cells of animals of the same species, the so-called auto-cytolysins.

Similarly the ovum of an animal is not permeable to the cytolysins contained in the spermatozoön of an animal of the same species. In order to bring about the development of the mature ovum the auto-cytolysin must be carried bodily into the egg. And that is the function of the motile spermatozoön.

This bold conception has received a striking though unintentional confirmation by the observations of Bataillon. He succeeded in 1910 in inducing parthenogenesis in frogs' eggs by simply pricking them with a needle, provided, as he found afterwards, that the needle carried with it a trace of the blood. He believes that it is the leucocytes which are introduced by the needle which cause the development. A few years previously Guyer in 1907 had obtained similar positive results by injecting frogs' eggs with the lymph or the blood from another frog.

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[1] Pieri, "Un nouveau Ferment soluble: l'Ovulase," *Archives de Zoologie Experimentale et Generale*, vol. xxix., 1899.

[2] Dubois, "Sur la Spermase et l'Ovulase," *Comptes Rendus de la Soc. de Biol.*, vol lii., 1900.

[3] Winkler (H.), "Über die Furchung unbefruchteter Eier unter der Einwirkung von Extraktivstoffen a. d. Spermata," *Nachrichten der kgl. Gesellschaft der Wissenschaften zu Göttingen*, Mathemat.-Phys. Klasse, 1900.

[4] Gies, "Do Spermatozoa contain an Enzyme having the Power of Causing Development of Mature Ova?" *Amer. Jour. of Physiol.*, vol. vi., 1901.

[5] Quoted from Loeb, *Dynamics of Living Matter*.

Loeb's work has proved of great heuristic value and has attracted many workers to this fascinating field of cyto-chemistry. A very interesting historical account of the whole subject together with a very full bibliography is given by F. R. Lillie in his book, "Problems of Fertilisation."[1] He criticises some of Loeb's conclusions and contributes a new hypothesis. It is based mainly on the observation that mature eggs of *Arbacia* and certain other invertebrates, when suspended in sea-water, secrete a substance which agglutinates the spermatozoa of the same species. It is a specific reaction and is given only by mature eggs, and neither by fertilised eggs nor by immature eggs. The jelly membrane of the eggs is saturated with this substance, which Lillie calls "fertilisin." It has the physical characters of a colloid, being non-dialysable, and is very heat resistant; when allowed to act on spermatozoa it disappears from the solution if not present in excess. It possesses a considerable degree of specificity if tested against spermatozoa belonging to different species. Its action on the spermatozoa is to agglutinate the heads of the spermatozoa which swell, while the tails remain unaffected. The adhesive property which the sperm develops under these circumstances binds the egg to the sperm, and is evidence of an intimate chemical combination of sperm- and egg-constituents beginning at the very moment of union. The presence of the agglutinating substance is necessary for the activation of development in the egg of the sea-urchin, and Lillie suggests that as the result of the interaction of this substance with the head of the spermatozoa a substance is formed or released which activates the egg. "The spermatozoön is conceived, by means of a substance which it bears and which enters into union with the fertilisin of the egg, to release the activity of this substance within the egg."

Other workers look upon physical changes occurring in the colloids of the ovum as the essential processes causing development. Thus Yves Delage[2] looks upon the membrane formation which precedes segmentation of the egg as a coagulation or gelation. This is followed by disappearance of the nuclear membrane which he interprets as a liquefaction or degelation. He therefore devised a very successful method of artificial parthenogenesis in which the application of a coagulative agent, namely tannic acid, is followed by treatment with a liquefying agent, namely ammonia.

Wolfgang Ostwald[3] has determined the amounts of oxidising ferments present in the ovaries and testes of toads, frogs, and newts. The watery extracts of these organs had the power of decomposing hydrogen peroxide with the formation of water and oxygen, and of oxidising guaiaconic acid to guaiacum blue, so that a blue colour appeared when these extracts were added to an emulsion of guaiac resin. These reactions indicate the presence of a catalase and of a peroxidase in the extracts of the sexual glands. Such ferments are present in many, if not all, organs and tissue fluids. but a special significance is attributed by Ostwald to their presence in the ova and spermatozoa, because he found the spermatozoa to contain more catalase and more peroxidase than the ova, and because the activity of these ferments—especially the peroxidase—is increased when the extracts of ova are mixed with the extracts of spermatozoa.

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[1] Lillie (F.), *Problems of Fertilisation*, University of Chicago Press, 1919.

[2] Delage and Goldsmith, *La Parthénogenèse naturelle et expérimentale*, Paris, E. Flammarion, 1913.

[3] Wolfgang Ostwald, "Über das Vorkommen von oxydativen Fermenten in den reifen Geschlechtszellen von Amphibien und über die Rolle dieser Fermente bei den Vorgängen der Entwicklungserregung," *Biochem. Zeitsch.*, vol. vi., 1907.

The development of the ovum after fertilisation is, according to Ostwald, due to this activation of the oxidising ferments inducing a chemical synthesis of nuclein substances and leading to the formation of the astrosphere. According to the view of Fischer and Ostwald,[1] which is, however, not accepted by other workers,[2] the formation of the astrosphere initiates cell-division, and therefore the development of the egg.

The investigations on artificial parthenogenesis show that it is possible to replace the developmental function of the spermatozoön by physico-chemical means. But the spermatozoön has also the hereditary function of transmitting the paternal characters to the developing embryo by fusing its nuclear material with that of the ovum. One must distinguish, therefore, clearly between these two functions of the spermatozoön. There is evidence that these two functions depend upon different materials in the spermatozoön and that even when an ovum is fertilised by a spermatozoön only one of these two functions may operate, namely the developmental one, while the hereditary function remains inoperative. Loeb succeeded in inducing experimental hybridisation between two widely different species, the egg of a sea-urchin and the sperm of a starfish, by placing them in slightly alkaline sea-water. The plutei which developed were in every point identical with the pure breed of the sea-urchin (*Strongylocentrotus purpuratus*). Other workers have obtained similar results in other animals. A very striking case is that observed by Hertwig and based on the fact that exposure of spermatozoa to radium damages them. The damage can be graded in such a way that the spermatozoön can still enter the egg, but its nucleus is no longer able to fuse with the egg nucleus. The eggs then develop into larvæ. Other experiments on hybridisation by various authors have shown that under certain conditions development may be initiated by spermatozoa belonging to a different species without the occurrence of a fusion between the sperm nucleus and the egg nucleus. The resulting larvæ are then purely maternal and have half the number of chromosomes. In other words: it is possible to induce parthenogenesis by the spermatozoön.

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[1] Fischer and Ostwald, "Zur Physikalisch-Chemischen Theorie der Befruchtung," *Pflüger's Arch.*, vol. cvi., 1905.

[2] See, for instance, Burrian, *loc. cit.*

CHAPTER IX

THE TESTICLE AND THE OVARY AS ORGANS OF INTERNAL SECRETION

> "Da muss sich manches Räthsel lösen,
> Doch manches Räthsel knüpft sich auch."
> —GOETHE.

THE principal evidence supporting the theory that the ovary and testicle are organs of internal secretion is derived from the experimental study of the effects produced, first, by removing these organs, and, secondly, by transplanting them to abnormal positions in the body. Experiments of such a kind clearly demonstrate the influence of the ovary and testicle upon the growth and development of the other generative organs, and upon many of the secondary sexual characters. They indicate, moreover, that the nature of this influence is chemical rather than nervous. Certain further evidence, which is less satisfactory in character, has been obtained from experiments on the injection of ovarian and testicular extracts.[1]

THE CORRELATION BETWEEN THE TESTIS AND THE OTHER MALE ORGANS AND CHARACTERS

It has already been recorded (p. 251) that the removal of the testes in adult life brings about a gradual atrophy of the prostate gland. It has also been shown that this operation, if performed prior to puberty, prevents the development of the prostate, whereas division of the vas deferens and the abolition of sperm production have no arresting influence.[2] One-sided castration produces no effect, the retention of a single testis being sufficient to maintain the functional activity of both prostate glands. Similarly it has been stated that Cowper's glands are probably dependent upon testicular influence for their growth and activity (p. 252).

More remarkable is the close correlation that exists between the testes and the secondary sexual characters of the male—that is to say, those characters which are found only in the male sex, but are not directly connected with the organs of generation.

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[1] For general accounts and references to literature see Harms, *Experimentelle Untersuchungen über die Innere Sekretion der Keimdrüsen*, Jena, 1914; Lipschütz, *Die Pubertätsdrüse und ihre Wirkungen*, Berne, 1919; and Gley, *Les Sécrétions Internes*, Paris, 1914.

[2] Wallace (C.), *Prostatic Enlargement*, London, 1907. It is shown also that vasotomy has no influence on the growth and activity of the prostate.

Thus, it is notorious that castration before puberty in man prevents the growth of hair on the face, arrests the development of the male chest and pelvis, and preserves the high-pitched voice of boyhood by hindering the growth of the larynx, while at the same time it exercises a marked influence over the mental characteristics.[1] It is equally well known that at the time of puberty, when the testes begin to assume their functional activity, there is a corresponding development of the secondary sexual characters, both in man and in a large number of animals. This correlation appears to be still closer in those animals in which the increased testicular activity that takes place in the breeding season is associated with a periodic development of other sexual characters. Thus, in the male elephant the glands on the side of the face emit a musky secretion during rut.

Darwin,[2] in elaborating his theory of sexual selection, collected together numerous examples of secondary sexual differences occurring in animals of various kinds. Cunningham, in a work upon "Sexual Dimorphism," has cited a number of further cases,[3] in many of which the structural peculiarities in question are shown to be closely correlated with the essential organs of reproduction.

The effects of castration in the stag, for example, are discussed at some length by Cunningham, Morgan,[4] and other writers. If the testes are removed in quite immature animals the antlers never develop, even the knobs failing to make an appearance. If castration is performed in stags whose antlers have just commenced to develop, these remain covered by skin, forming the so-called peruke antlers, which are not shed or renewed. If the operation is carried out after the complete development of the antlers, these are shed prematurely and are replaced in the next season by incomplete antlers with a tendency towards peruke formation, and these, on being thrown off, are not renewed. Partial castration in the immature stag is said to result in a weaker horn formation; but the effect is general, and shows no restriction to the side on which the testis is wanting.[1]

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[1] According to Hikmet and Regnault ("Les Eunuques de Constantinople," *Bull. et Mém. de la Soc. d'Anthropologie de Paris*, vol. ii., 5th series, 1906), the eunuchs of Constantinople have the following mental characteristics :—They are avaricious, illogical, obstinate (*i.e.* cannot change their ideas), have no judgment, accept information without proof ; are not cruel, but fond of children and animals ; are faithful in their affections, but have no courage ; their mental activity is very slight, and they are extremely fanatical. Senility is premature, but the teeth are kept solid and white. For skeletal differences in eunuchs, see below, p. 323. See also Kammerer, "Ursprung der Geschlechtsunterschiede," *Fortschr. naturwiss. Forschung von Abderhalden*, 1912 ; and Hirschfeld, *Sexuale-Pathologie*, Bonn, 1917.

[2] Darwin, *The Descent of Man*, Popular Edition, London.

[3] Cunningham (J. T.), *Sexual Dimorphism in the Animal Kingdom*, London, 1900 ; "The Heredity of Secondary Sexual Characters in Relation to Hormones," *Arch. f. Entwick.-Mech.*, vol. xxvi., 1908 ; *Hormones and Heredity*, London, 1921. See also Hegar, *Korrelationem der Keimdrüsen und Geschlechtsbestimmung*, 1893 ; and Sellheim, "Zur Lehre von den sekundären Geschlechtscharakteren," *Beiträge zu Geburtsh. u. Gynäk.*, vol. i., 1898.

[4] Morgan, *Experimental Zoology*, New York, 1907.

The results of castration in the fallow deer have been investigated by Fowler,[2] who summarises his results under five headings: (1) Complete castration at birth limits the horn formation to the development of single dugs; (2) Castration in mature life tends to produce asymmetry in the growth of the horns; (3) The antlers of castrated deer are often shed prematurely if the operation is performed after they have lost the velvet, but antlers which have grown after castration may be retained for over two years; (4) Incomplete castration shortly after birth is followed by a weak development of the antlers, which are otherwise normal; (5) One-sided castration may result in the abnormal or incomplete development of one antler, the other antler being nearly normal. The last point would seem to require confirmation.[3]

In the prong-buck (*Antilocapra americana*), which is the only hollow-horned Ruminant that periodically sheds its horns, the effects of castration are also quite distinct. The horns, instead of rising vertically as in normal individuals, curve forwards from the roots, and then bend downwards and backwards so as to terminate in incurved points in the close vicinity of the eyes. The anterior tine is almost completely suppressed. The horn-sheath is never shed, and as a consequence a composite sheath is developed, and this seems to go on growing as long as new sheaths are formed from the horn-core.[4]

It is interesting to note that in the eland, in which both sexes possess horns, the development of these structures is not appreciably affected by castration. A similar statement may be made about some horned cattle, in which (in common with other cattle) castration in early life produces changes in the general proportions of the body.

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[1] These statements are based chiefly upon the results of Caton's experiments with Wapiti and Canadian deer (Caton, *Antelope and Deer of America*, 2nd Edition, New York, 1881. See also Holdich, "Exhibition of Antlers of Deer showing Arrest of Development due to Castration," *Proc. Zool. Soc.*, 1905). Some further examples of sexual correlation are given in Chapter I. of this work. (See Morgan, *loc. cit.*) Professor Seligman informs me that stags which fail to grow antlers (*i.e.* occasional "sports") have well-developed testicles.

[2] Fowler, "Notes on some Specimens of Antlers of the Fallow Deer, etc.," *Proc. Zool. Soc.*, 1894.

[3] MacEwen (*The Growth and Shedding of the Antlers of the Deer*, Glasgow, 1920) refers to another case of one-sided castration being followed by asymmetrical horn growth.

[4] Pocock, "The Effects of Castration on the Horns of the Prong-buck," *Proc. Zool. Soc.*, 1905. It is to be noted that horns are occasionally present in the female prong-buck.

In the sheep, also, castration during immaturity brings about changes in the bodily conformation. Thus, in breeds in which the males only are horned, the skulls of the wethers may resemble the females rather than the males.[1] This is the case with the Merino sheep. In the Herdwick it has been shown that not only is the presence of the testes necessary for the initiation of horn growth, but for its continuation, the horns ceasing to grow forthwith after castration and at any stage of horn development. Further, unilateral castration does not inhibit the growth of the horns which develop symmetrically in the normal manner.[2]

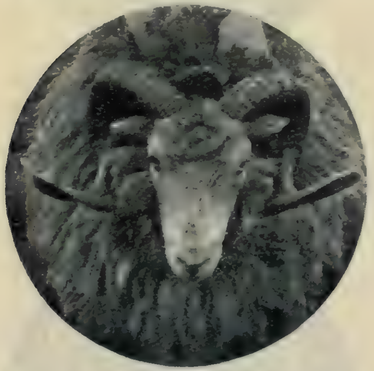

Fig. 76.—Herdwick ram (normal). (From Marshall and Hammond, *Jour. of Physiol.*)

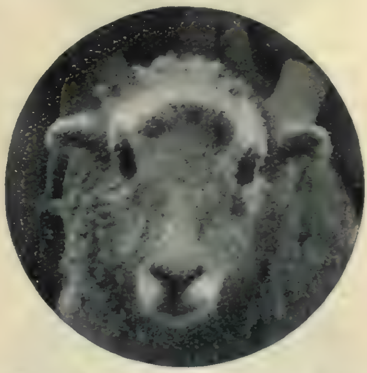

Fig. 77.—Herdwick wether (castrated young). (From Marshall and Hammond, *Jour. of Physiol.*)

Differences in the form of the body have been noted in eunuchs as well as castrated animals. Thus, the bones of the limbs tend to be longer than the normal, producing a condition of gigantism. This is due to an arrest in the ossification of the epiphyses (which is one of the effects of castration). The same phenomena have been described in castrated guinea-pigs, oxen, capons, and various animals.[3]

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[1] Seligman, "Exhibition of a Skull of a Domestic Sheep which had been Castrated when Young," *Proc. Zool. Soc.*, 1906. Changes in conformation as a result of early castration have also been described in other animals.

[2] Marshall, "On the Effects of Castration and Ovariotomy upon Sheep," *Proc. Roy. Soc.*, B., vol. lxxxv., 1912. Marshall and Hammond, "On the Effects of Castration on Horn Growth in Sheep," *Jour. of Physiol.*, vol. xlviii., 1914. In the Merino also castration is known to arrest the growth of the horns of the ram (Arkell and Davenport, "Horns in Sheep, etc.," *Science*, vol. xxxv., 1912).

[3] Lannois and Roy, "Des Relations qui existent entre l'État des Glandes génitales males et le Développement du Squelette"; and Poncet, "De l'Influence de la Castration sur le Développement du Squelette," *C. R. de la Soc. de Biol.*, vol. lv., 1902. See also Pittard, *C. R. de l'Acad. des Sciences*, vol. cxxxix., 1904, who gives statistics showing that there is often an increase in size in eunuchs,

It is well known that caponisation or the removal of the testes in fowls arrests the development of the comb and some other secondary male characters which are normally present in the cock. Recent experiments upon this subject are described below in dealing with

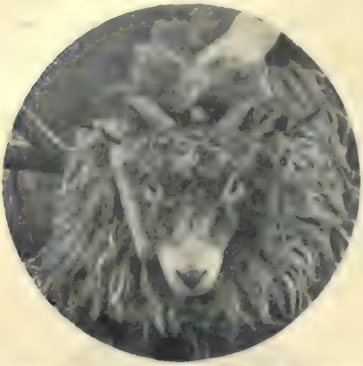

Fig. 78.—Herdwick wether castrated when four months old. The horns are the same length as they were at the time of castration. (From Marshall and Hammond, *Jour. of Physiol.*)

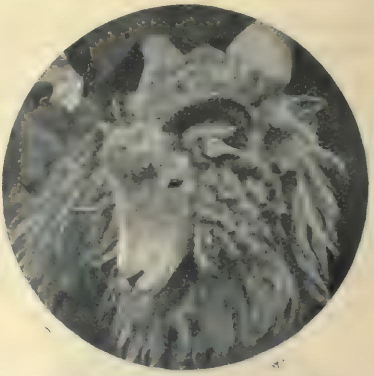

Fig. 79.—Herdwick wether castrated five months after birth. The horns ceased to grow after castration. (From Marshall and Hammond, *Jour. of Physiol.*)

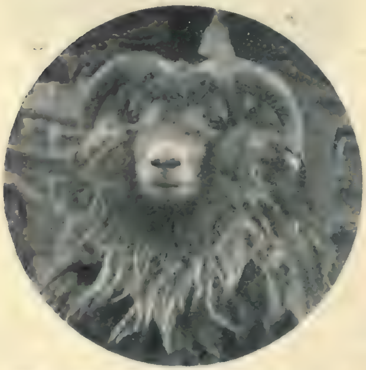

Fig. 80.—Herdwick ram lamb from which one testis was removed four months after birth. The horns continued to grow and were symmetrical. (From Marshall and Hammond, *Jour. of Physiol.*)

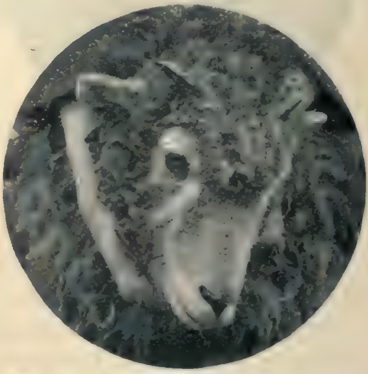

Fig. 81.—Herdwick wether from which the testes were removed four months after birth but the epididymes retained. The horn growth ceased after castration. (From Marshall and Hammond, *Jour. of Physiol.*)

especially in the legs. For accounts of other anatomical differences in eunuchoid persons, see Duckworth, *Jour. of Anat. and Phys.*, vol. xli., 1906, and Tandler and Gross (*Arch. f. Entwick.-Mech.*, vol. xxvii., 1909). The latter authors discuss the general effects of castration on the organism. See also Geddes, "Abnormal Bone Growth in the Absence of Functioning Testicles," *Proc. Roy. Soc. Edin.*, vol. xxxi., 1910.

the results of testicular transplantation or the injection of testicular extracts. Other instances of the effects of castration are briefly referred to by Darwin.[1]

Secondary sexual characters, however, are not always correlated with the essential organs of reproduction. For example, castration in the horse does not arrest the development of the withers—the gelding, in this respect, resembling the stallion rather than the mare, in which the withers are lower.[2]

In Arthropods the correlation between the secondary sexual characters and the generative glands appears to be far less close than it is among Vertebrates. Thus, Oudemans[3] showed that the removal of the testes from the male caterpillar of *Ocneria dispar* had no influence on the development of the secondary male characters, these being normal. Kellogg[4] performed a similar experiment on the caterpillar of the silkworm moth and obtained a like result. Crampton[5] grafted the heads of caterpillars of one sex upon the bodies of individuals of the opposite sex, and found that the generative organs had no influence upon the development of the secondary sexual characters of the transplanted heads. Moreover, Meisenheimer[6] found that in caterpillars artificially made hermaphrodite (by transplanting ovaries into males or testes into females) the original males always developed into butterflies with typical secondary male characters in spite of the fact that living ovaries were present, while the original females always developed into normal female butterflies. The sexual instincts were also unmodified by the presence of the grafted gonads. With castrated or spayed individuals into which gonads of the opposite sex were successfully transplanted the effects were similar, the somatic characters of the original sex being unmodified.[7] Regen[8] who removed the gonads from larval crickets

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[1] Darwin, *loc. cit.* Sellheim (*Beiträge zur Geburtshülfe und Gynäk.*, vol. i., 1898, and vol. ii., 1899) states that there is an increase in the size of the skull, pelvis, and leg-bones in castrated cocks. According to Berizowiski (*Arch. Zellforsch.*, vol. ii., 1911), castration in mice causes elongation and broadening of the cells of the intestinal epithelium, but this would seem to need confirmation.

[2] Wallace, *Farm Live-Stock of Great Britain*, 4th Edition, London, 1907. Williams (W. L.) says there are no sexual differences in the bones of the pelvis of the horse (*Veterinary Obstetrics*, New York, 1917).

[3] Oudemans, "Falter aus Castraten Raupen," *Zool. Jahrbücher*, vol. xii., 1899.

[4] Kellogg, "Influence of the Primary Reproductive Organs on the Secondary Sexual Characters," *Jour. of Exp. Zool.*, vol. i., 1904.

[5] Crampton, "An Experimental Study upon Lepidoptera," *Arch. f. Entwick.-Mechanik*, vol. vii., 1898.

[6] Meisenheimer, *Experimentelle Studien zur Soma- und Geschlechts-Differenzierung*, Part I., Jena, 1909.

[7] Kopec, "Nochmals über die Unabhängigkeit der Ausbildung sekundären Geschlechtscharaktere von den Gonaden bei Lepidopteren," *Zool. Anz.*, vol. xliii., 1913. See also Kammerer, *loc. cit.*

[8] Regen, "Kastration und ihre Folgerscheinungen bei *Gryllus campestris*," *Zool. Anz.*, vols. xxxiv. and xxxv., 1909 and 1910.

(*Gryllus campestris*), found that the castrated males chirped like normal ones and mated with the females, and the spayed females behaved like unoperated ones and bored holes in the ground although they were unable to lay eggs in them.

In spider crabs attacked by *Sacculina* the gonads disappear, and in the total absence of the testis secondary sexual characters of the female type are found in a large percentage of cases; but this change in the direction of the opposite sex may set in prior to the complete disappearance of the testes. The change is manifested in the appearance of the egg-bearing abdominal sac appendages, which have no representatives in the male.[1] Potts states that in the hermit crab infected by a similar *Peltogaster*, the modifications of the male which occur are of the same type, and are maintained after the atrophy of the testis, and cannot be necessarily consequent on the presence of a secretion of the testis.[2]

In both these cases it would seem that the modifications which take place are brought about independently by changes in the general metabolism. This appears to be so also with so-called parasitic castration in insects, for the gonads are not necessarily affected.

In the male common shore crab it was found that the testis underwent very little diminution after infection by *Sacculina*, but that the male approximated to the female type. The change, however, was less marked than in the cases referred to above, in which parasitic castration was almost or quite complete.[3]

It would appear, therefore, that whereas many of the secondary sexual characters are closely associated with the presence of the genital glands, there are others which develop independently of any influence from the organs of reproduction.

Berthold seems to have been the first to put forward the view that the testis is an organ of internal secretion which is responsible for the development of the secondary sexual characters.[4] He based his theory upon the results of testicular transplantation in fowls in which the testes, after removal, were attached to new positions and still sufficed for the development of the sexual characters. In attributing this rôle to the testes, Berthold appears also to have been the first to assign an endocrine function to any bodily organ, thus anticipating Claude Bernard and the numerous physiologists who have succeeded him.

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[1] Smith (Geoffrey), "Rhizocephala, Fauna and Flora of the Gulf of Naples," *Monograph* xxix., Berlin, 1906.

[2] Potts, "The Modification of the Sexual Characters of the Hermit Crab, caused by the Parasite *Peltogaster*," *Quar. Jour. Micr. Science*, vol. l., 1906; and "Some Phenomena Associated with Parasitism," *Parasitology*, vol. ii., 1909.

[3] Potts, "Observations on the Changes in the Common Shore Crab caused by *Sacculina*," *Proc. Camb. Phil. Soc.*, vol. xv., 1909. Upon recovery from parasitic castration ova may be formed in what were the testes. This has been shown by Smith to happen with *Inachus*. Smith states that the parasite *Sacculina* forces the crabs to elaborate a fatty or yolk material similar to that which the normal female produces when the ovary is ripening. See also Smith's "Studies in the Experimental Analysis of Sex," *Quar. Jour. Micr. Science*, vols. lvi. and lvii., 1910 and 1911. For the results of experimental or parasitic castration in other Arthropods and groups of Invertebrates, see Lipschutz, *loc. cit.*

[4] Berthold, "Transplantation der Hoden," *Arch. f. Anat. u. Physiol.*, vol. xlii., 1849. According to Berman (*The Glands regulating Personality*, New York, 1921) the idea was advanced by Bordeu in the eighteenth century.

It was not till some years later that Brown-Séquard[1] elaborated the theory that the testis exercises an influence upon the general metabolism through the internal secretion produced by it. He based his conclusion to a large extent upon the beneficial effects which he believed to accrue from the administration of testicular extracts. These extracts were supposed to possess invigorating properties, and could be usefully employed in cases of deficiency of testicular substance, or in old age, when the testes lose their functional activity. It is not unlikely that some of the effects which Brown-Séquard attributed to the use of the extract were in reality due to suggestion.

The idea of a connection between testicular influence and invigoration or rejuvenescence has lately been revived with reference to the interstitial gland of the testis, and it has been claimed that successful transplantation of this tissue into the aged has been followed by beneficial results. Thus, Steinach[2] has described experiments upon rats, which, after reaching a condition of senility and impotency and with the vesiculæ seminales and other accessory male organs undergoing atrophy, were restored to a state of vigour and functional activity by the transplantation of interstitial testicular tissue. Rejuvenescence could also be brought about as a result of vasectomy, an operation which, as described below, results in the eventual atrophy of the seminiferous tissue, but in the persistence or even hypertrophy of the interstitial or "puberty gland," and according to Steinach the same effects are produced by vasectomy in aged men. In confirmation of Steinach, Sand[3] records an experiment upon a dog which showed every sign of senility and decrepitude, but after the operation of bilateral vasectomy was rejuvenated and restored to a state of robust vigour.

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[1] Brown-Séquard, "Du Rôle physiologique et thérapeutique d'un Suc extrait de Testicules," *Arch. de Physiol.*, 1889.

[2] Steinach, *Verjüngung durch experimentelle Neubelebung der Alternden Pubertätsdrüse*, Berlin, 1920 (reprinted from *Arch. f. Entwicks.-Mech.*, vol. xlvi., 1920). According to the penal laws of Indiana (1907), California and Connecticut (1909), in the United States of America, vasectomy may be carried out on male criminals in order to prevent them propagating, while at the same time not impairing their normal masculine vigour. I am indebted to the late Viscount Bryce, at one time H.M. Ambassador to the United States of America, for information on this subject (see Sharp, *Jour. Amer. Med. Assoc.*, 4th December 1909). If Steinach is correct in believing that increased vigour and prolongation of life may be a result of vasectomy, the policy of which these laws are the outcome is one of doubtful wisdom. At any rate some other way of inducing sterility might be adopted.

[3] Sand, "Vasectomie pratiquée chez un Chien, etc.," *C. R. de Soc. de Biol.*, vol. lxxxv., 1921.

Voronoff has made a similar claim for the interstitial tissue of the testis and appears to regard the hormone secreted by this gland as the veritable "elixir of life." The body is pictured as a battle-ground in which there is a prolonged struggle between the "primitive cells" (represented by those of the connective tissue) and the "specialised cells" which show an intenser metabolic activity, and senescence indicates the progress of the former, with death as their complete victory. The internal secretory organs exercise a regulating influence on the combat, and more especially the interstitial gland, for the atrophy or loss of this leads to a rapid victory by the connective tissue cells. The eunuchs of Egypt are cited as evidence of the truth of this view, and a number of experiments upon animals are referred to or described, and, as in Steinach's memoir, photographs and other illustrations are shown representing animals (sheep, goats, etc.) displaying all the signs of senescence, and then later after a successful testicular graft had had a sufficient time to work its rejuvenating influence upon the metabolism.[1] A possible fallacy in all such experiments is the effect of nutritional or any environmental influence other than that of the graft, and the conclusions reached must at present be accepted with caution.

Lichtenstern[2] states that the prejudicial effects of castration in man may be remedied by a successful testicular graft, and this is believed to be due to the influence of the puberty gland.

Steinach[3] had previously found that in rats in which the testes were removed and successfully transplanted into the abdominal cavity the penis and accessory male organs developed normally.

Poehl[4] claims to have prepared from the testis a substance having the chemical composition represented by the formula $C_5H_{14}N_2$. He believes this substance, which he calls spermine, to be the active principle of Brown-Séquard's testicular extract, stating that it has a beneficial influence over the metabolism of the body and acts as a physiological tonic (see p. 299).

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[1] Voronoff, *Vivre*, Paris, 1920. This work contains reprints of histological papers by Retterer as an Appendix.

[2] Lichtenstern, "Behebung von Kastrationsfolge beim Menschen durch Transplantation von cryptorchen Hoden," *Münch. med. Woch.* (19), 1916. See also Steinach and Lichtenstern, "Umstimmung der Homosexualität durch Austausch der Pubertätsdrusen," *Münch. med. Woch.* (21), 1918. For further testicular transplantation results in man, see abstracts of papers by Stanley and Kelker, and others in *Endocrinology*, vols. i.-iv., 1918-21.

[3] Steinach, "Geschlechtstrieb und echt sekundäre Geschlechtscharactere," *Zent. f. Physiol.*, vol. xxiv., 1910.

[4] Poehl, "Weitere Mitteilungen über Spermin," *Berliner klin. Wochenschrift*, 1891.

Zoth,[1] and also Pregel,[2] state that they have obtained evidence by ergographic records of the stimulating action of testicular extracts upon the neuro-muscular apparatus in the human subject. They are of opinion that the injection of such extracts results in a decrease of nervous and muscular fatigue, and at the same time diminishes the subjective fatigue sensations.

The composition and physiological properties of testicular extract have also been investigated by Dixon,[3] who found it to contain proteins, organic substances unaltered by boiling, and inorganic salts. Nucleoprotein was especially plentiful. Injection into the circulation caused a fall of blood pressure due chiefly to cardiac inhibition, but no very striking or interesting results.

Walker[4] appears to be dubious about the efficacy of testicular medication, stating that the injection of fluid extract into castrated dogs had no effect in arresting the atrophy of the prostate gland (*cf.* de Bonis, see Chapter VII., p. 251). It is possible, however, that the "active principle" of the testicular secretion was destroyed in the preparation of the extract, and that the constant administration of fresh testicular substance might have led to a different result. In these experiments extract of the whole gland seems to have been used and not of the interstitial gland only.

Bouin and Ancel[5] showed in the horse and other animals that when the vasa deferentia are ligatured the spermatogenetic tissue of the testis ceases to be functional and gradually undergoes degeneration, while the interstitial cells remain unaffected. They pointed out, further, that those cells have a distinctly glandular appearance, and that their presence suffices for the development of the secondary sexual characters. Consequently they drew the conclusion that the testis is an organ producing an internal secretion which is elaborated by the interstitial cells and not by the spermatogenic tissue. Copeman,[6] as a result of similar experiments, reached an identical conclusion. Ancel and Bouin stated, further,[1] as a result of a series of experiments upon guinea-pigs, that the subcutaneous injection of extract prepared from the interstitial tissue of the testis prevented the effects which castration otherwise would have produced upon the rest of the generative system and upon the skeleton.[2] Their results, therefore, differ from those of Walker. In another paper Bouin and Ancel[3] state that the injection of similarly prepared testicular extract in guinea-pigs tends to promote growth. In the horse they found that the development of the interstitial gland substance of the adult coincided with the first occurrence of spermatogenesis; but that there was also a fœtal interstitial gland, which disappeared at the end of gestation, and a slightly developed gland composed of xanthochrome cells, which was only found in the immature animal.[4]

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[1] Zoth, "Zwei ergographische Versuchsreihen über die Wirkung orchitischen Extractes," *Pflüger's Arch.*, vol. lxii., 1896.

[2] Pregel, "Zwei weitere ergographische Versuchsreihen, etc.," *Pflüger's Arch.*, vol. lxii., 1896.

[3] Dixon, "A Note on the Action of Poehl's Spermine," *Jour. of Physiol.*, vol. xxv., 1900; "The Composition and Action of Orchitic Extracts," *Jour. of Physiol.*, vol. xxvi., 1901. According to Hervieux, the interstitial gland of the testis contains a ferment which splits neutral fats, and converts dextrin, maltose, and glycogen into glucose but has no action on lactose (*C. R. de la Soc. Biol.*, vol. lx., 1906).

[4] Walker (G.), "Experimental Injection of Testicular Fluid, etc.," *Johns Hopkins Hospital Bulletin*, vol. xi., 1900.

[5] Bouin and Ancel, "Recherches sur les Cellules interstitielles du Testicule des Mammifères," *Arch. de Zool. Expér.*, vol. i., 4th series, 1903.

[6] Copeman's experiments, which were upon the rabbit, were not published, but were personally communicated to Swale Vincent, and alluded to by him in a lecture on "Internal Secretion and the Ductless Glands," *Lancet*, 1st August 1906. See also Copeman, "Experiments on Sex Determination," *Proc. Zool. Soc.*, 1919.

Tandler and Gross[5] have described the effects of subjecting the testes to the influence of the Röntgen rays. They found that in the roebuck the spermatogenetic tissue is destroyed but the interstitial tissue is unaffected, and in correlation with this the horns develop as in the normal male. Leo Loeb[6] found that in guinea-pigs with undescended testes the interstitial cells were present, and although spermatogenesis[7] did not go on, sexual desire was manifested. Secondary male characters, however, might be absent, the animal showing female somatic characters (see p. 346). Whitehead[8] from a study of abnormal testes likewise found that the sexual instinct was associated with the existence of the interstitial cells. The present writer[9] found as a result of an experimental investigation in the hedgehog that the growth of the accessory organs (vesiculæ, etc.)

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[1] Bouin and Ancel, "Action de l'Extrait de Glande interstitielle du Testicule etc.," *C. R. de l'Acad. des Sciences*, vol. cxlii., 1906.

[2] Castration in early life, as already mentioned, is said to lead to a prolonged retention of the cartilaginous unions between the bones, especially in those of the limbs.

[3] Bouin and Ancel, "Sur l'Effet des Injections de l'Extrait de la Glande interstitielle du Testicule sur la Croissance," *C. R. de la Soc. de Biol.*, vol. lxi., 1906.

[4] Bouin and Ancel, "La Glande interstitielle du Testicule chez le Cheval," *Arch. de Zool. Expér.*, vol. iii., 4th series, 1905. According to Lécaillon the interstitial tissue in the mole's testis is functionally active during the breeding season, when the testis is sixty-four times larger than during the resting period. ("Sur les Cellules interstitielles du Testicule de la Taupe considérées en dehors de la Période de Reproduction," *C. R. de la Soc. de Biol.*, vol. lxvi., 1909.)

[5] Tandler and Gross, *Die Biologischen Grundlagen der Sekundären Geschlechtscharaktere*, Berlin, 1913.

[6] Loeb, "Relations between the Interstitial Gland of the Testicle, Seminiferous Tubules and the Secondary Sexual Characters," *Biol. Bull.*, 1918.

[7] See p. 164, Chapter V.

[8] Whitehead, "A Peculiar Case of Cryptorchism, etc.," *Anat. Record*, vols. ii. and iii., 1908 and 1909.

[9] Marshall, "The Male Generative Cycle in the Hedgehog: with Experiments on the Functional Correlation between the Essential and Accessory Sexual Organs," *Jour. of Physiol.*, vol. xliii., 1911.

appeared to be correlated with the seasonal development of the interstitial tissue and not with the seminiferous tubules. Vasectomy and one-sided castration did not inhibit the seasonal growth of the accessory organs (see above, p. 246). Rasmussan has found that in the woodchuck both spermatogenetic and interstitial tissue increased rapidly in March and April after hibernation, after which the former continued to display activity, while the latter began to undergo retrogression (April to June) and remained ill-developed throughout the rest of the year.[1] Lécaillon[2] has made similar observations on the mole.

Of very great importance are Steinach's transplantation experiments with rats and guinea-pigs, not only on account of the evidence they show as to the secretory influence of the gonads, but because of their bearing on the question of sex-determination. The latter subject is dealt with in a later chapter. Steinach[3] showed that if the testes are removed from the normal position and transplanted under the skin, notwithstanding that their ordinary nerve connections are non-existent, the copulatory organ, vesicula, and other accessory male organs develop normally. Since the transplanted testes consist of interstitial cells only, and these are sufficient to cause the male characters to develop, Steinach designates this tissue the "puberty gland." Moreover Steinach found that testes transplanted into a young female, from which the ovaries had been removed, caused the clitoris to develop into a penile structure, besides stimulating the animal's growth and producing manifestations of sexual desire as in the male. Such individuals he regards as being sexually inverted or masculinised. Steinach carried out converse experiments with ovarian transplantation which are described below.

Lipschütz[4] has studied the structure of the hypertrophied clitoris in the guinea-pig after masculinisation by means of a transplanted testis, and found it to contain normal corpora cavernosa penis as well as the two quill-shaped horny spikes which are found normally in the intromittent sac of the male (see p. 258). Sand,[1] too, has described hypertrophy of the clitoris in the masculinised rat. The latter author has carried out a series of experiments upon the ligaturing and section of the vas deferens and upon artificially produced cryptorchism (or the condition in which the testis is retained in the body cavity, brought about by Sand by occluding the inguinal canal). These experiments confirm the importance of the interstitial or puberty gland. Experiments upon the transplantation of the gonads and upon sex reversal have also been carried out by Moore,[2] and these, together with other experiments by Sand on the same subject, are described below in the chapter on sex determination.

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[1] Rasmussan, "Seasonal Changes in the Interstitial Cells, etc.," *Amer. Jour. of Anat.*, vol. xxii., 1917. "Cyclic Changes in the Interstitial Cells, etc.," *Endocrinology*, vol. ii., 1918.

[2] Lécaillon, *loc. cit.*

[3] Steinach, "Untersuchungen zur Vergleichenden Physiologie der Männlichen Geschlechtsorgane," *Pflüger's Arch.*, vol. lvi., 1894; "Geschlechtstrieb und echt Sekundäre Geschlechtsmerkmale als Folge der Innersekretorischen Funktion der Keimdrüsen," *Zent. f. Phys.*, vol. xxiv., 1910; "Umstimmung des Geschlechtscharakters bei Säugethieren dursch Austausch der Pubertätsdrüsen," *Zent. f. Phys.*, vol. xxv., 1911; "Willkürliche Umwandlung von Säugethier-Männchen, etc.," *Pflüger's Arch.*, cxliv., 1912; "Feminierung von Männchen und Maskulierung von Weibchen," *Zent. f. Phys.*, vol. xxvii., 1913; "Pubertätsdrüsen und Zwitterbildung," *Arch. f. Entwick.-Mech.*, vol. xlii., 1916. Steinach and Holzknecht, "Erhöhte Wirkungen der inneren Sekretion bei Hypertrophie der Pubertätsdrüsen," *Arch. f. Entwick.-Mech.*, vol. xlii., 1916. Steinach and Kammerer, "Klimak und Mannbarkeit," *Arch. f. Entwick.-Mech.*, vol. xlvii., 1921.

[4] Lipschütz, "Umwandlung der Clitoris, etc.," *Arch. f. Entwick.-Mech.*, vol. xliv., 1918. "On the Internal Secretion of the Sexual Glands," *Jour. of Physiol.*, vol. li., 1917. *Die Pubertätsdrüse und ihre Wirkungen*, Bern, 1919. This book contains further information and many references.

It has often been stated that an imperfectly descended testicle in man, notwithstanding the fact that it may be without any spermatogenic function, is nevertheless of the greatest benefit to its possessor in virtue of its influence over the metabolism. "The secondary sexual characters are a far more exact measure of the value of the testicular tissues than are the presence of spermatozoa in the external secretion. It may almost be said that a man's male plumage is in direct proportion to the weight or amount of testicular tissue present."[3] Since the retained or cryptorchid testicle comes to consist mainly or entirely of interstitial tissue we have here further evidence that this gland is the organ of the internal testicular secretion.[4] Lipschutz[5] has shown that in the guinea-pig after partial castration a portion of testicular tissue one-sixteenth the normal size is sufficient to admit of the development of the secondary sexual characters, and he ascribes this result to the functional activity of the interstitial tissue.

Shattock and Seligmann[6] have described the results of occluding the vasa deferentia in Herdwick rams and in fowls, and these point in the same direction. The animals operated upon acquired full secondary characters. The authors suppose, therefore, that the development of these characters is not brought about by metabolic changes induced by a nervous reflex arising from the function of sperm ejaculation.

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[1] Sand, "Experiments on the Internal Secretion of the Sexual Glands, especially on Experimental Hermaphroditism," *Jour. of Physiol.*, vol. liii., 1919; *Experimentelle Studien over Kφnskarakterer hos Pattedyr*, Copenhagen, 1918; "Études Experimentales, etc.," I., II., and III., *Jour. de Phys. et Path. Gén.*, 1921 and 1922.

[2] Moore (A.), "On the Physiological Properties of the Gonads, etc.," *Jour. of Exp. Zool.*, vols. xxviii. and xxxiii., 1919 and 1921.

[3] Corner, *Diseases of the Male Generative Organs*, Oxford, 1907. See also McAdam Eccles, *The Imperfectly Descended Testis*, London, 1903.

[4] For further information and references see Biedl, *The Internal Secretory Organs*, English Translation, London, 1917.

[5] Lipschutz, "Sur les Conséquences de la Castration partielle," *C. R. de la Soc. de Biol.*, vol. lxxxiii., 1920.

[6] Shattock and Seligmann, "Observations upon the Acquirement of Secondary Sexual Characters, indicating the Formation of an Internal Secretion by the Testicle," *Proc. Roy. Soc.*, vol. lxxiii., 1904. The same investigators also attempted to obtain further evidence by grafting together two cocks, one castrated and the other normal, but these experiments were unfortunately a failure, one of the birds always dying after a short time. (*Trans. Path. Soc.*, vol. xlvi., 1905.)

Foges[1] has described the effect of removing the testes of fowls and transplanting them to abnormal positions in the body cavity. In the successful experiments it was found that the presence of functional transplanted testes exercised the same influence over the development of the secondary sexual characters as testes growing in the normal position, and that the appearance of "capon" characters was averted, the comb, wattle, spurs, etc., being developed as in uncastrated cocks. Foges concludes that the testes are organs of internal secretion, and control the development of the male characters.

Shattock and Seligmann have also described the effects of testicular transplantation and incomplete caponisation in fowls. In certain cases the testes are stated to have broken up during the operation, so that minute fragments were retained, sometimes being left in the normal position, and sometimes becoming dislocated and attached to the adjacent viscera or to the abdominal wall. Although these pieces of testicular substance continued to produce spermatozoa, they were virtually ductless glands.[2] In such cases the secondary sexual characters of the cock developed to a varying extent which seemed to depend upon the amount of testicular substance left behind. "One must regard the external character of maleness as a quantity which varies proportionately with the amount of gland tissue present" (but see p. 338).

According to Loewy,[3] the injection of testicular substance into young capons causes the development of normal male skeletal characters, as well as a better growth of the comb, etc. Furthermore, Walker[4] states that, in two experiments in which he injected saline extract of cocks' testicles into two hens daily for several months, the combs and wattles grew in size and became more brightly coloured, reaching a maximum in five months. When the injections were discontinued, the combs and wattles underwent shrinkage and eventually became reduced almost to their original condition. Geoffrey Smith,[1] however, on repeating the experiments, obtained negative results, and is of opinion that the effects obtained by Walker were really those of normal periodic growth.

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[1] Foges, "Zur Lehre der secundären Geschlechtscharaktere," *Pflüger's Arch.*, vol. xciii., 1903. For an account of an earlier and less complete investigation see Hanau, "Versuche über den Einfluss der Geschlechtsdrüsen, etc.," *Pfluger's Arch.*, vol. lxv., 1897. See also Sellheim (*loc. cit.*), who says that the weight of the brain is slightly less in the capon (see above, p. 325). And see Cunningham, *loc. cit.*

[2] Confirmed by Mackenzie and the author (unpublished experiments).

[3] Loewy, "Neuere Untersuchungen zur Physiologie der Geschlechtsorgane," *Ergebnisse der Phys.*, vol. ii., 1903.

[4] Walker (C. E.), "The Influence of the Testis upon the Secondary Sexual Characters of Fowls," *Proc. Roy. Soc. Med.*, vol. i., 1908.

The effects of castration in the cock are thus summed up by Morgan[2] who bases his description mainly upon the results obtained by Goodale[3]: "The feathers are little changed; some of them, the hackles especially, become longer. The lowermost tier of wing coverts are elongated as compared with those of the cock. The spurs are practically the same in the capon and cock. The capon is disinclined to give voice, but at times he crows. The moulting is not affected. The size of the capon is larger. He pays little attention to the hens. He is not pugnacious, and if attacked will not often fight. As a rule, he does not pursue the hens, but if a hen squats down as the capon approaches he will mount and go through the characteristic mating reaction. The comb is extremely small, much smaller than that of the female of the same race; it is infantile rather than feminine."

Pézard's results[4] are similar. He found castration inhibited the growth of the erectile organs (comb, wattles, etc.), the capacity to crow, and the fighting instincts, etc. The spurs and general plumage were not affected. Castration in pheasants led to practically identical results. In a general way castration in the male and ovariotomy in the female produced a neutral type identical in each case. Injection of interstitial testicular extract prepared by aqueous maceration of gland of pig caused the comb, etc., to grow completely, but with the cessation of the injections regression took place. By grafting testicular tissue on to a castrated hen rapid growth of the comb could be induced. Injections into castrated males caused similar results, the fighting instinct being regained.

The question as to the precise elements responsible for the production of the internal testicular secretion is discussed by Morgan and by Pézard. The former investigator was the first to show that in Sebrights and some other varieties of poultry in which the cocks are often "hen-feathered" castration resulted in the development of male plumage and the suppression of the racial "henny" characteristics.[1] In such strains Boring[2] found that cells resembling the luteal cells of the mammalian ovary were present in the testes, but that they were absent in normal adult cock birds. It was concluded, therefore, that castrating the Sebright produces its effect by the removal of these luteal cells which were held to be responsible for the suppression of cock-feathering. Pease,[3] however, has been unable to find any distinction between normal and henny-feathered cocks in the matter of testicular luteal cells. In the testes of immature birds or birds in which spermatogenesis was only beginning, luteal cells could always be found in both normal and hen-feathered, but in testes showing active spermatogenesis no luteal cells were seen. Pease, therefore, is disposed to believe that Morgan and Boring are not justified in associating luteal cells with hen feathering, and suggests that they may be a source of food for the sperms which are in process of formation. Boring and Pease both found luteal cells in the ovary of the female. Boring had previously arrived at the conclusion that there are no "interstitial cells in the testes of the domesticated chicken in

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[1] Smith, "Studies on the Experimental Analysis of Sex," Part 5, *Quar. Jour. Micr. Science*, vol. lvi., 1911.

[2] Morgan, *The Genetic and Operative Evidence relating to Secondary Sexual Characters*, Carnegie Inst. (Washington) Pub. No. 285, 1919.

[3] Goodale, *Gonadectomy*, Carnegie Inst. (Washington) Pub. No. 243, 1916.

[4] Pézard, "Le Conditionnement Physiologique des Caractères Sexuels Secondaires chez les Oiseaux," Thesis, University of Paris, 1918. See also *Comptes Rend. de l'Acad. Sci.*, 1911, 1917, 1918, 1919, and 1920. Pézard states (1919) that an exclusively meat diet with cocks leads to genital atrophy and castration results. For the "Numerical Law of Regression of Certain Secondary Sex Characters," see *Jour. Gen. Phys.*, vol. iii., 1921.

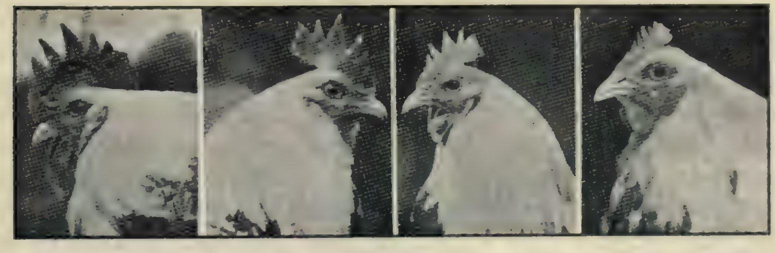

Fig. 82.—Successive stages in the regression of the comb of the cock after castration: (*a*) at the time of castration; (*b*) five weeks after; (*c*) seven weeks after; (*d*) when regression was complete. (From Pézard.)

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[1] This observation has been confirmed by the present writer working in conjunction with Professor R. C. Punnett. It was found further that after the removal of one testis only in hen-feathered cocks, "cocky" feathering may develop on the operated side of the bird. This result may have been due to injury to sympathetic nerve ganglia. Punnett suggests, however, that in one bird it may have been a case of premature development of such feathering, which in the non-occurrence of an operation would have grown at the next moult, since hen-feathered cocks sometimes do subsequently develop an intermediate type of feathering. (See Punnett and Bailey, "Genetic Studies in Poultry," III., *Jour. of Genetics*, vol. xi., 1921. *Cf.* Bond, "On a Case of Unilateral Development of Secondary Male Characters in a Pheasant, etc.," *Jour. of Genetics*, vol. iii., 1914.)

[2] Boring, "The Interstitial Cells and the supposed Internal Secretion of the Chicken Testis," *Biol. Bull.*, vol. xxiii., 1912; "Sex Studies," *Jour. of Exp. Zool.*, vol. xxv., 1918. See also Boring and Pearl, "Sex Studies," *Anat. Record*, vol. xiii., 1917; and Boring and Morgan, "Luteal Cells and Hen-Feathering," *Jour. of Gen. Phys.*, vol. i., 1918.

[3] Pease, "Note on Professor T. H. Morgan's Theory of Hen Feathering," *Proc. Camb. Phil. Soc.*, vol. xxi., 1922.

the sense that this term has been previously used," and that no internal secretion is produced by interstitial tissue. Pézard[1] believes that the internal secretion of the testes in birds is localised in the germinative cells or in the elements of Sertoli.

Des Cilleuls[2] found that in the cock the appearance of interstitial cells coincided with that of the secondary male characters, and that they increase synchronously; also that the cock characters were well marked at a time when the seminiferous tubules were still embryonic. Thomsen[3] states that the secondary sexual characters are established in the chick before hatching. Boring found that interstitial connective tissue is very abundant in the testes of newly hatched chicks, but, as mentioned above, there was no evidence of secretory function. Reeves[4] observed interstitial tissue in cocks of 5½, 9, and 18 months. The whole question as to the seat of production of the internal testicular secretion in birds still seems to be obscure.

Goodale[5] has described the effects of removal of the testes in the duck. The Rouen drake throughout most of the year has the nuptial plumage which is assumed after the autumn moult. It is in striking contrast to the plumage of the female, the head being green, and the breast claret colour, and there are four curved tail feathers. The breeding season ends in July when the drake assumes the "eclipse" plumage which is very similar to that of the female. The head becomes brown and the four tail sex feathers become straight. The eclipse plumage lasts until the autumn moult in October. In the mallard it continues somewhat longer. If, however, castration is performed the eclipse plumage does not appear. This case seems somewhat similar to that of the hen-feathered cocks described above. Shattock and Seligmann state that when female wild duck assume the male plumage the spurious males undergo the seasonal eclipse, although this may be incomplete and aberrant. The same authors observe also that the periods of activity and non-activity in the testis of the wild duck, as far as spermatogenesis is concerned, do not correspond with seasonal changes in the plumage.

Duerden states that the red skin coloration of the cock ostriches of North and South Africa as well as the rich dark blue of the southern variety are dependent upon the presence of the testes, but that the castrated cock attains the normal black plumage which distinguishes it from the hen.[1]

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[1] Pézard, *loc. cit.*

[2] Des Cilleuls, "Apropos du Determinisme des Caractères Sexuel Secondaires chez les Oiseaux," *Compt. Rend. de la Soc. de Biol.*, vol. lxxiii., 1912.

[3] Thomsen, "Die Differenzierung des Geschlechts und das Verhältnis der Geschlechten beim Hühnchen," *Arch. f. Entwick.-Mech.*, vol. xxxi., 1911.

[4] Reeves, "On the Presence of Interstitial Cells in the Chicken's Testis," *Anat. Record*, vol. ix., 1915.

[5] Goodale, "Some Results of Castration in Ducks," *Biol. Bull.*, vol. xx., 1910; *Gonadectomy*, Carnegie Inst. (Washington) Pub. No. 243, 1916. See also Shattock and Seligmann, "Observations made to ascertain whether any Relation subsists between the Seasonal Assumption of the Eclipse Plumage in the Mallard and the Functions of the Testicle," *Proc. Zool. Soc.*, 1914.

Further evidence that the testis produces an internal secretion is supplied by Nussbaum[2] as a result of his experiments upon frogs. At the approach of the breeding season there is formed in the male frog a thickened pad of skin on the first digit of each fore limb associated with an increased muscular development in the fore arm. This modification is preparatory to the act of copulation, when the male frog uses its arms in embracing the female, and so assists in pressing out the eggs from the oviduct (see p. 20). If the male frog be castrated, the pad is not formed and the muscles fail to develop. Nussbaum found that, if pieces of testis from another frog were grafted into the dorsal lymph sac of a frog previously castrated, the secondary sexual characters of the latter developed just as in a normal frog. The transplanted testes, however, after exerting their influence in the way described, underwent a gradual absorption.

Nussbaum stated, further, that when the nerves supplying the first digit were severed, the pad did not develop, this operation being performed on a normal frog. Similarly if the nerves supplying the clasping muscle of the fore arm were severed, the enlargement did not occur. He concluded, therefore, that the internal secretion formed in the testis had a specific action upon certain local groups of ganglion cells, and that the nerves passing from these to the fore arm and digit convey a stimulus which induces the growth of the muscle and that of the thickened pad. In support of the view that the testis exerts its influence upon the metabolism (at least partially) through the medium of the nervous system, Nussbaum cites an observation of Weber, according to whom an hermaphrodite finch, having an ovary on one side of the body and a testis on the other, showed the characteristic female coloration on the ovarian side and the male plumage on the side of the testis.

Nussbaum's conclusion has been controverted by Pflüger,[3] who points out that in other cases the apparent effect of section of nerves is due to loss of sensibility in the parts affected, in consequence of which the tissues are not guarded from injury, and further, that the secondary sexual characters of animals are usually arranged symmetrically. The effect produced by one-sided castration is general rather than local, and the operation has little or no influence in destroying the symmetry of the sexual characteristics (*cf.*, however, Fowler's statement about fallow deer, which appears to be exceptional). It is probable, therefore, that Pflüger is correct in supposing that the internal secretion of the testis acts as a direct stimulus upon the cells of the frog's arm and so induces the development of the sexual pad and the hypertrophy of the muscle.[1]

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[1] Duerden, "Crossing the North African and South African Ostrich," *Jour. of Genetics*, vol. viii., 1919. The skin of the hen and young bird of both sexes is grey. Spayed hens assume the black plumage of the cock (see below, p. 344). *Cf.* Fitzsimons, "A Hen Ostrich with the Plumage of a Cock," *Agric. Jour. University of South Africa*, vol. iv., 1912.

[2] Nussbaum, "Innere Sekretion und Nerveneinfluss," *Merkel and Bonnet, Ergeb. der Anat. und Entwick.*, vol. xv., 1905.

[3] Pflüger, "Ob die Entwicklung der sekundären Geschlechts-charaktere vom Nervensystem abhängt?" *Pflüger's Arch.*, vol. cxvi., 1907.

Meisenheimer[2] has confirmed the results of Nussbaum's experiments on castration and testicular transplantation in the frog, but Smith and Schuster,[3] who have repeated the experiments, while admitting that the castration effect occurs, were sceptical about the efficiency of the grafts, their own transplantation experiments being negative. The latter authors further criticise Nussbaum and Meisenheimer's conclusions, stating that "the effect of castration, except actually during the breeding season, is to make the papillæ on the thumb-pads remain essentially in the condition they were at the time of castration." Meisenheimer's claim to have induced hypertrophy as a result of ovarian transplantation they regard as quite unproved.

According to Kammerer[4] the pad can develop in the breeding season in *Alytes* in individuals previously castrated.

There is some evidence to show that, after one-sided castration, the remaining testis is capable of undergoing a compensating hypertrophy,[5] and according to Ancel and Bouin[6] and others there is a compensatory enlargement of the interstitial gland. Lipschütz[7] has thrown some doubt on this conclusion, pointing out that a very small fragment of testicular tissue suffices for the development and maintenance of the sexual characteristics, as shown both by himself and by Pézard, and stating that the hypertrophy of such tissue (*e.g.* after the removal of one whole testis and a great part of the second one), when such hypertrophy occurs, is due to local conditions of nutrition (*i.e.* of blood supply), and is not truly compensatory. The two views are not necessarily inconsistent, since with other organs of internal secretion (*e.g.* the pancreas) it is known that a small portion of gland tissue will suffice for the needs of the organism, and yet such organs will sometimes undergo what appears to be a compensatory regeneration. Moreover, if a minute portion of gland tissue is really in every way adequate, it is difficult to understand why the glands in question (whether testis, or pancreas, or any other endocrine organ) should be as large as they normally are. It is not unreasonable to assume, therefore, that the endocrine organ of the testis when artificially reduced tends to undergo an hypertrophy to its normal bulk, but that this hypertrophy is dependent upon local nutritive conditions or blood supply. It must be pointed out, however, that some investigators (Kyrle,[1] Kohn, Stieve, etc.) are disposed to deny an endocrine function to the interstitial tissue, suggesting that it exercises a trophic function in connection with seminiferous cells, or hold with Pézard that the testicular hormone is produced by the germinative tissue or the cells of Sertoli. That a condition in which the male sexual characters have failed to develop may be associated with the presence of interstitial cells is not unknown, but Lipschütz[2] has pointed out that the mere existence of these cells is insufficient, and that to be effective the interstitial tissue must be in a state of functional activity, whereas this is not always the case.

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[1] See also Nussbaum, "Hoden und Brunstorgane, etc.," *Pflüger's Arch.*, vol. cxxvi., 1909. For further references to the literature of testicular transplantation, see Boruttau, "Innere Sekretion," in Nagel's *Handbuch der Physiologie des Menschen*, Braunschweig, 1906; and Harms, *Experimentelle Untersuchungen uber die innere Sekretion der Keimdrüsen*, Jena, 1914.

[2] Meisenheimer, "Ueber die Wirkung von Hoden- und Ovarial Substanz auf die Sekundären Geschlechtsmerkmale des Frosches," *Zool. Anz.*, vol. xxxviii., 1911.

[3] Smith and Schuster, "Studies in the Experimental Analysis of Sex," Part 8, *Quar. Jour. Micr. Science*, vol. lvii., 1912.

[4] Kammerer, "Vererbung Erzwungener Formveränderungen, etc.," *Arch. f. Entwick.-Mechanik*, vol. xliv., 1919.

[5] Ribbert, "Beiträge zur kompensatorischen Hypertrophie, etc.," *Arch. f. Entwick.-Mechanik*, vol. i., 1894.

[6] Bouin and Ancel, "Recherches sur le Rôle de la Glande Interstitielle, etc.," *C. R. de l'Acad. Sci.*, vol. cxxxvii., 1903; "La Glande Inst., etc.," *C. R. de l'Acad. Sci.*, vol. cxxxviii., 1904; "De la Glande, etc.," *Jour. de Phys. et Path.*, vol. vi., 1904.

[7] Lipschütz, Ottow, Wagner, and Bormann, "On the Hypertrophy of the Interstitial Cells in the Testicle of the Guinea-pig, etc.," *Proc. Roy. Soc.*, B., vol. xciii., 1922.

It has already been mentioned that, according to Ancel and Bouin and others, there is a fœtal interstitial gland in the testis of the developing horse and also in the chick. It would seem probable that this gland is responsible for the development of the pre-natal sexual characters in the manner postulated by Lillie in his theory of the "free-martin." This theory has recently received remarkable confirmation from the experiments of Minoura, who was able to produce artificial "free-martins" in the chick by grafting portions of reproductive gland, obtained from other individuals, on to the chorio-allantoic membrane during the progress of development. This work is described below in the chapter on the Determination of Sex (p. 695).

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[1] Kyrle, "Ueber die Regenerationsvorgänge im tier- und menschlicher Hoden," *Sitzungsber. Akad. Wiss. Wien*, vol. cxx., 1911. See also Kohn, *Arch. f. Entwick.-Mechanik*, vol. xlvii., 1920; Stieve, *Ergebn. d. Anat. u. Entwick.*, vol. xxiii., 1921; and Tiedje, *Deuts. med. Woch.*, No. 13, 1921.

[2] Lipschütz, "Ralentissement expérimentale de la Masculinisation," *C. R. de la Soc. de Biol.*, vol. lxxxvi., 1922.

THE CORRELATION BETWEEN THE OVARY AND THE OTHER FEMALE ORGANS AND CHARACTERS

It has long been known that the ovary, like the testis, exerts a profound influence over the metabolism, and that the extirpation of this organ, no less than castration in the male, leads to very distinct results. In the human female double ovariotomy, if carried out before puberty, besides preventing the onset of puberty and the occurrence of menstruation, produces noticeable effects on the general form and appearance, as may be seen in adult women in semi-barbarous parts of Asia, where the natives perform this operation upon young girls. Such women are said to be devoid of many of the characteristics of their sex, and in certain cases to present resemblances to men.

In some female animals, also, the removal or incomplete development of the ovaries has been said to lead to the appearance of male characters. For example, Rörig[1] records three cases in which female deer possessed horns, and were found upon examination to show abnormalities in the ovaries. Darwin[2] also states that female deer have been known to acquire horns in old age.[3]

Better instances of this kind of phenomenon have been recorded from among poultry, game birds, and ducks, which, on growing senile, have been observed to acquire some of the secondary male characters. Darwin[4] refers to the case of a duck which, when ten years old, assumed the plumage of the drake. He also mentions an instance of a hen which in old age acquired the secondary sexual characters of the cock. Hunter[5] described a case of a hen pheasant which had male plumage correlated with an abnormal ovary, and many other such instances have been recorded. Gurney[6] states that the assumption of male plumage is frequently (but not invariably) associated with barrenness in female gallinaceous birds but not as a rule in passerine birds. The phenomenon has been observed in black grouse, capercaillie, wild duck, widgeon, merganser, and various other species belonging to different orders. On the other hand, Gurney records instances of a hen chaffinch with male plumage and an unlaid egg, a hen redstart with male plumage and a number of developing eggs, as well as similar cases of hen pheasants. The male plumage may be only temporarily assumed. Further examples of the assumption of male plumage by hen birds are recorded by Shattock and Seligmann,[1] who describe the phenomenon under the name of allopterotism. Some of these cases are regarded as of the nature of partial hermaphroditism. It would appear possible that the secondary male characters are normally latent in the female, and that the ovaries exert an inhibitory influence over their development. On the other hand, there is no clear evidence that castration in the male animal leads to the assumption of female characters, excepting in a negative sense (*i.e.* excepting in so far as it inhibits the development of male characters).

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[1] Rörig, "Ueber Geweihentwickelung, etc.," *Arch. f. Entwick.-Mechanik*, vol. x., 1900. **For sheep, see final footnote, p. 392.**

[2] Darwin, *Variation in Animals and Plants*, Popular Edition, London, 1905.

[3] Smith (F.) (*Veterinary Physiology*, 3rd Edition, London, 1907) states that female cats, whose ovaries have been removed while young, acquire a head of the male type (with well developed tissues in the jowl, the exact converse occurring in castrated males). Herbst, who also discusses this question (*Formative Reize in der Tierischen Ontogenese*, Leipzig 1901), expresses the belief that the gonads in either sex exercise a definite inhibitory influence, preventing the appearance of the secondary sexual characters of the opposite sex.

[4] Darwin, *loc. cit.*

[5] Hunter (J.), "Account of an Extraordinary Pheasant," *Phil. Trans.*, vol. lxx., 1780.

[6] Gurney, "On the Occasional Assumption of Male Plumage by Female Birds," *Ibis*, vol. vi., 5th series, 1888.

The operation of complete ovariotomy is difficult in birds owing to the diffuse condition of the ovary and the close proximity of the vena cava, and in de-sexing pullets (or converting them into "poullardes") the usual practice is to remove a portion of the oviduct or destroy in some other way its functional relation with the ovary.[2] This operation is believed to favour growth and fattening, but the result may be due simply to the fact that the albumen and the other products of oviducal secretion are no longer produced.

According to Brandt,[3] the absence of a functional oviduct may be correlated with male characters and a normal ovary, this being stated to be the case in a specimen of *Ruticilla phœnicurus*, but such a fact seems on the face of it unlikely excepting on the assumption that a partial hermaphroditism existed.

Goodale[4] was the first completely to remove the ovary from a bird, and by employing brown Leghorn fowls in which sexual differentiation is very marked he obtained very clear results. It was only in young birds that the ovary was sufficiently compact to make the operation practicable. In the successful experiments the hen assumed the full plumage of the Leghorn cock, with red back, black breast, and long pointed hackle and saddle feathers. Spurs also developed. The comb and wattles developed irregularly. The birds did not crow.

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[1] Shattock and Seligmann, "An Example of True Hermaphroditism in the Common Fowl, with Remarks on the Phenomena of Allopterotism," *Trans. Path. Soc.*, vol. lvii., 1906. "An Example of Incomplete Glandular Hermaphroditism in the Domestic Fowl," *Proc. Roy. Soc. Med.*, Path. Section, vol. i., (November) 1907.

[2] Wright, *The New Book of Poultry*, London, 1902. Laycock, *Nervous Diseases of Women*, London, 1840.

[3] Brandt, "Anatomisches und Allgemeines über die sogenannte Hahnenfedrigkeit und über anderweitige Geschlechtsanomalien bei Vögeln," *Zeitsch. f. wiss. Zool.*, vol. xlviii., 1899. This paper also cites numerous cases of hen birds assuming male plumage, and many references are given.

[4] Goodale, *Gonadectomy, etc.*, Carnegie Inst. (Washington) Pub., 1916.

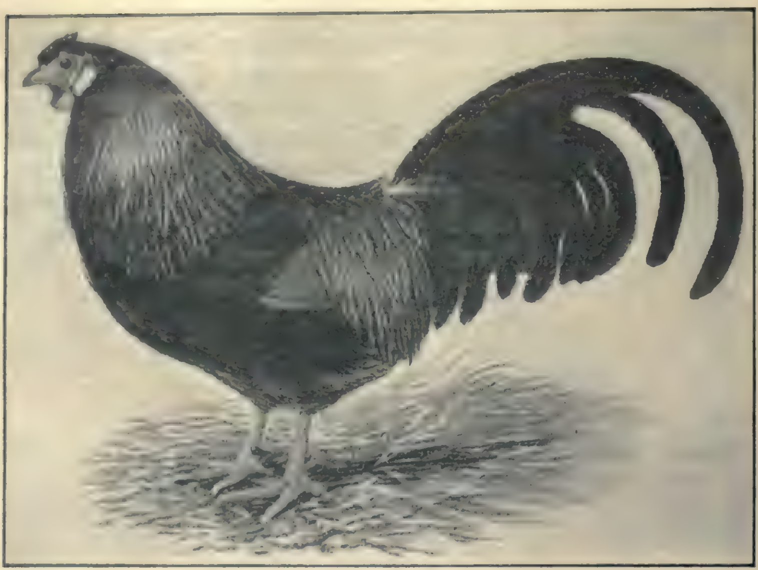

FIG. 83.—Ovariotomised brown Leghorn hen. (From Goodale.) The bird shows male feathering and spurs, but the comb and other erectile structures are not hypertrophied.

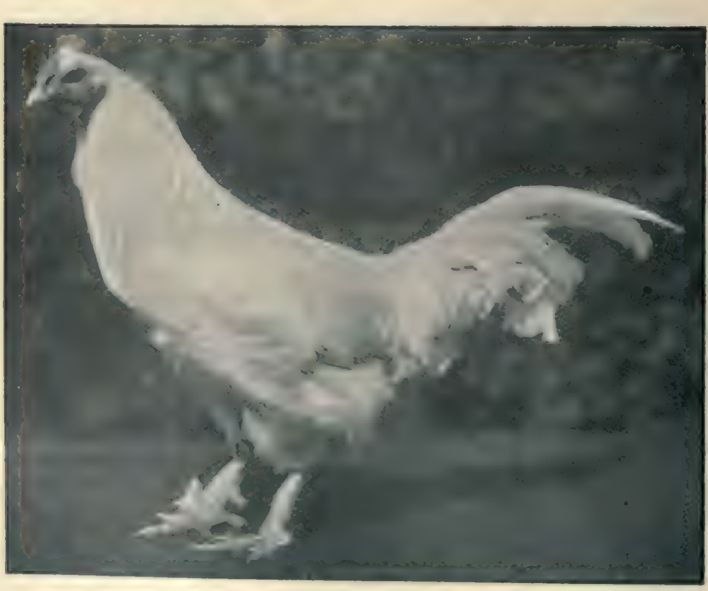

FIG. 84.—Ovariotomised pullet with plumage and spurs of male, *i.e.* of neutral type according to Pézard. (From Pézard.)

Pézard[1] obtained results on the whole similar, but concluded that ovariotomy had no influence on the development of the comb. Moreover, the sickle and other characteristically male feathers did not appear. The spayed hen Pézard regards as being a neutral type like the castrated cock (see above, p. 334). By transplanting ovarian tissue on to a castrated male the growth of the spurs, etc., could be inhibited and the bird become feminised. Goodale also has feminised a male bird by ovarian transplantation following on castration.

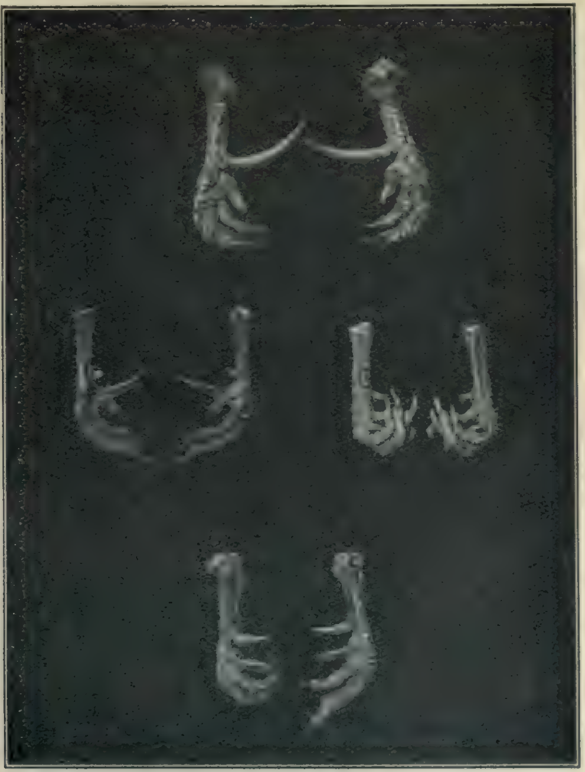

FIG. 85.—Successive stages in the growth of the spurs of a hen after ovariotomy: (left) six months after; (right) one year after; (bottom) two years after; (top) six years after. (From Pézard.)

Goodale removed the ovaries from ducks and found that the spayed female may or may not completely assume the perfect male plumage. One bird after complete ovariotomy did not even assume the eclipse plumage but retained the nuptial plumage of the drake.

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[1] Pézard, *loc. cit.* (see above, p. 334).

Another spayed duck first assumed the nuptial plumage and then the eclipse plumage of the breed in question, and this in turn (in autumn) was succeeded by the nuptial plumage again. Morgan[1] suggests that in the latter case a slight amount of ovarian tissue might have been retained.

Duerden[2] states that ovariotomy in the ostrich is followed by retention of the ordinary body colour, but that the normally grey feathers assume the blackness of the cock. This fact is taken advantage of by some African farmers, seeing that the plumage of the male is far more valuable economically than that of the hen. Thus the effects of castration in both male and female are to produce a similar type (see above, p. 337).

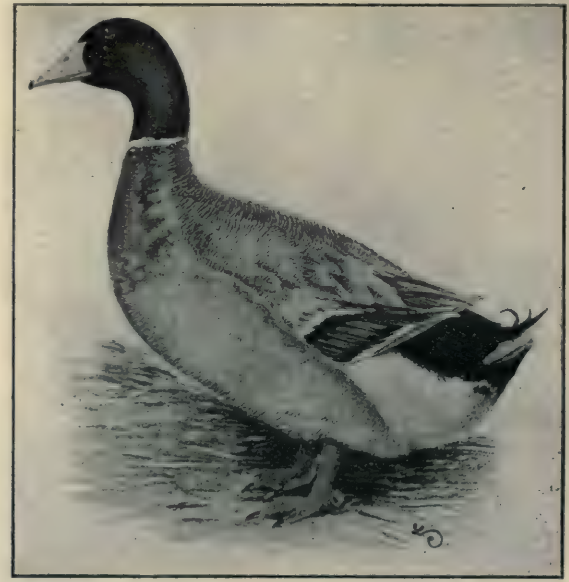

Fig. 86.—Normal Rouen drake. (From Goodale.)

The effect of ovariotomy upon the cow has been studied by Tandler and Keller[3] who state that it produces a type similar to the castrated male (that is to say, it causes a convergence of type in the manner described by Pézard for fowls). The height of the spayed animal is said to be less than that of the cow. The head is similar to the steer's head. Pearl and Surface[4] have recorded the assumption

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[1] Morgan, *loc. cit.*

[2] Duerden, *loc. cit.* (see above, p. 337).

[3] Tandler and Keller, "Die Körperform der Weiblichen Frühkastraten des Rindes," *Arch. f. Entwick.-Mech.*, vol. xxxi., 1910. For effect on cats, see above, footnote, p. 340. And see footnote, p. 358. For sheep, see final footnote, p. 392.

[4] Pearl and Surface, *Sex Studies*, VII., Orono, Maine, 1915.

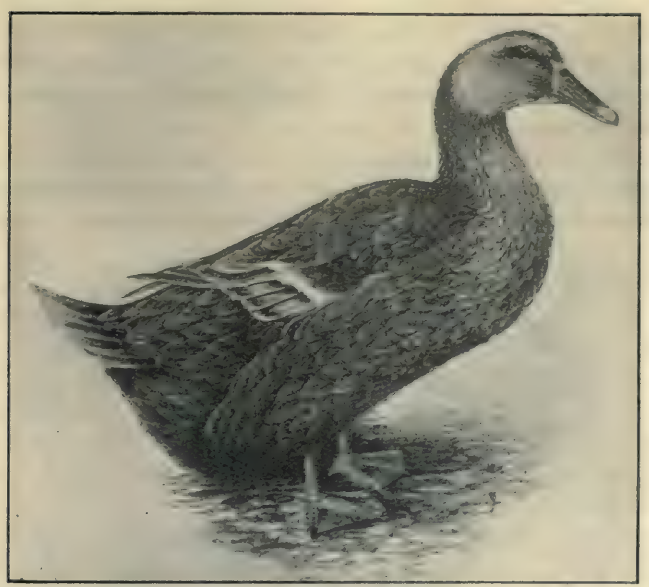

FIG. 87.—Normal Rouen duck. (From Goodale.) (*Cf.* Figs. 86, 88, and 89.)

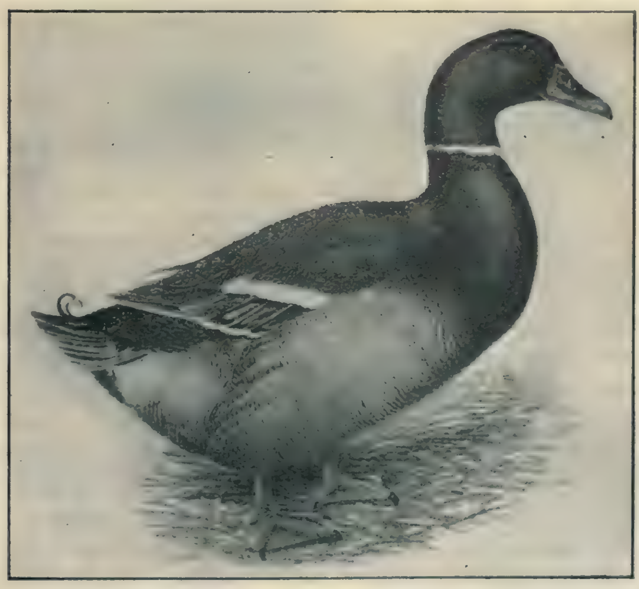

FIG. 88.—Ovariotomised Rouen duck—Type I.
(From Goodale.)

(*Cf.* Figs. 86, 87, and 89.) The bird was operated upon when six weeks old.

of male secondary characters by a cow previously normal after cystic degeneration of the ovaries. Since in this case the interstitial secreting mechanism of the ovaries was normal, it is suggested that the full development of secondary female characters is correlated with the corpus luteum.

Steinach has carried out a number of experiments on rats and guinea-pigs, producing the converse effect to that described above.[1] After transplanting the ovary into previously castrated males when they were young, very definitely female characters have developed. Most noteworthy was the growth of the mammary glands and teats, a feminised male guinea-pig yielding milk and suckling young ones. Moreover, the hair is said to have resembled that of the normal female, being finer and softer than in the normal male, and the size of the body was reduced. Lastly, the feminised animal reacted sexually like a female as shown especially by the "tail erect" reflex (normally concerned in coition) and the "kick guarding" reflex (used to keep off the male before the onset of œstrus). The follicles in the transplanted ovaries atrophied, but the interstitial cells (or "theca lutein" cells) remained, and these Steinach regards as representing

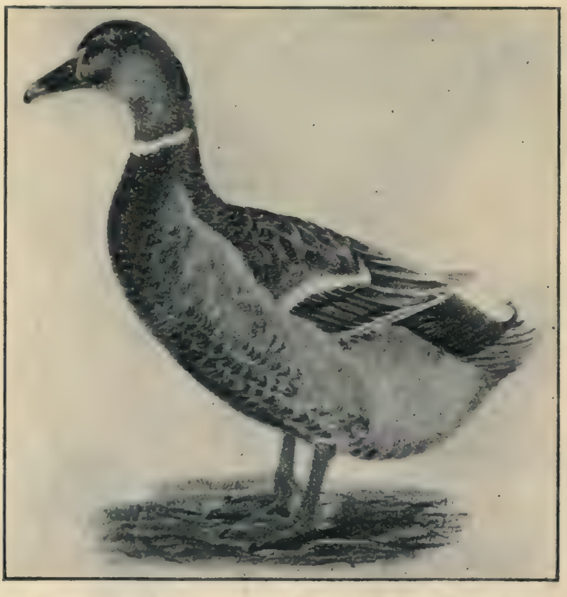

Fig. 89.—Ovariotomised Rouen duck—Type II. (From Goodale.)

(*Cf.* Figs. 86, 87, and 88.) The bird was operated upon when about a year old.

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[1] Page 331.

the "puberty gland" in the female.[1] When the ovaries in women are subjected to Röntgen ray treatment the climacteric does not supervene, and this is regarded as being due to the continued function of the puberty gland.[2] Athias and Sand[3] have also studied the development of the mammary glands and the secretion of milk in castrated males with ovarian grafts.[4]

The most obvious result of ovariotomy in women before puberty is that the uterus and oviducts remain infantile, and the breasts fail to develop.

Ovariotomy performed subsequently to puberty produces less marked results than when carried out in early life. The most noticeable effect is the cessation of menstruation, and this is sometimes accompanied by an atrophy of the breasts and a tendency towards obesity. Speaking generally, ovariotomy produces an artificial climacteric.

Most authorities are agreed that the uterus undergoes atrophy after the removal of the ovaries in adult life, and that castration in children and young animals arrests the development of the uterus.[5] These results are usually ascribed to the absence of ovarian influence, though a few authors seem disposed to dissent from this view (see below, p. 376). Thus, Hofmeir[6] and Benkiser[7] ascribe the degenerative changes to an insufficiency in the blood supply consequent upon the operation of removal, while Sokoloff[8] and Buys and Vandervelte[9] have supposed these changes to be due to a severance of nerves passing to the uterus.

In a series of experiments which were performed[10] upon the effects of ovariotomy in rabbits, it was found that the extent to which the degenerative process was carried was roughly proportional to the time which had elapsed between the operation and the killing of the animal. After an interval of six and a half months the uterus was found to be in a condition of pronounced fibrosis and to contain no glands. The epithelium was much attenuated, and the muscle fibres were broken up. A few small capillaries, however, could still be seen in the stroma. The Fallopian tubes also underwent atrophy. In other experiments in which the ovaries were removed from very young immature rabbits, which were killed after they had grown up, it was found that the uteri, although they had undergone slight development, were quite infantile, being no larger than those of rats. The Fallopian tubes were affected similarly. In all these experiments great care was taken to avoid interference with the blood supply to the uterus, the uterine branches of the pelvic vessels and the anastomotic branch of the ovarian artery being left uninjured. Furthermore, in certain other cases in which hysterectomy was performed instead of ovariotomy, and which, therefore, may be regarded as controls to the first series of experiments, the extirpation of the uterus had no arresting influence on the growth and nutrition of the ovaries (see p. 379).

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[1] For references, see p. 331.

[2] Steinach and Holzknecht, *loc. cit.*

[3] Sand, *loc. cit.*

[4] Athias, "L'Activité sécretoire de la Glande Mammaire hyperplasée chez le Cobaye Male Châtre consécutivement à la Graffe de l'Ovaire," *C. R. de la Soc. de Biol.*, vol. lxxviii., 1915.

[5] Kehrer, *Beiträge zur Klin. und Exper. Geburtskunde*, Giessen, 1877. Hegar, *Die Kastration der Frauen*, Leipzig, 1878. Sellheim, "Die Physiologie der Weiblichen Genitalien," *Nagel's Handbuch der Physiologie des Menschen*, vol. ii., Braunschweig, 1906. This article contains further references.

[6] Hofmeir, "Ernährung und Rückbildungsvorgänge bei Abdominaltumoren," *Zeitsch. f. Geburtsh. u. Gynäk.*, vol. v.

[7] Benkiser, *Verhandl. d. Deutsch. Gesell. f. Gynäk.*, Fourth Congress, 1891.

[8] Sokoloff, "Ueber den Einfluss der Ovarienextirpation auf Structurveränderungen des Uterus," *Arch. f. Gynäk.*, vol. li., 1896.

[9] Buys and Vandervelte, "Recherches Expérimentales sur les Lésions consécutives à l'Ovariotomie Double," *Arch. Ital. de Biol.*, vol. xxi., 1894.

[10] Carmichael and Marshall, "The Correlation of the Ovarian and Uterine Functions," *Proc. Roy. Soc.*, B., vol. lxxix., 1907. Bucura ("Beiträge zur inneren Funktion des weiblichen Genitals," *Zeitschr. f. Heilkunde*, vol. xxviii., 1907 ; and "Zur Theorie der inneren Sekretion des Eierstockes," *Zent. f. Gynäk.*, vol. xxxvii., 1914) obtained similar results with rabbits, and Tandler and Keller (*loc. cit.*) with cows. See also Shattock (*Proc. Roy. Soc. Med.*, Path. Sect., 1910)

Other and more conclusive evidence in support of the theory that the ovary is an organ of internal secretion is supplied by the results of various attempts to transplant ovaries in Mammals. The cases of Morris, Glass, Dudley, and Cramer, who transplanted ovaries from one woman to another, are described below in discussing the causes of the menstrual function (p. 360).

Knauer[1] has described experiments upon rabbits in which he removed the ovaries from the normal position and grafted them upon the mesometrium or between the fascia and the muscle of the abdominal wall. He found that they could be successfully implanted on both peritoneum and muscle, but that some portion of the grafted ovary invariably died. The rest, however, remained functionally active, and continued to produce ova which were capable of being fertilised. Knauer states that whereas castration in female rabbits produced a premature menopause, the uterus undergoing atrophy, this result was prevented by a successfully transplanted ovary. Knauer also experimented upon dogs and obtained similar results.

Grigorieff,[2] Ribbert,[3] and Rubinstein[4] carried out experiments

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[1] Knauer, "Die Ovarien-Transplantation," *Arch. f. Gynäk.*, vol. lx., 1900. See also *Cent. f. Gynäk.*, vol. xx., 1896.

[2] Grigorieff, "Die Schwangerschaft bei Transplantation der Eierstöcke," *Central. f. Gynäk.*, vol. xxi., 1897.

[3] Ribbert, "Über Transplantation von Ovarien, Hoden, und Mamma," *Arch. f. Entwick.-Mechanik*, vol. vii., 1898.

[4] Rubinstein, "Extirpation beiden Ovarien," *St. Petersburg Mediz. Wochenschr.*, 1899.

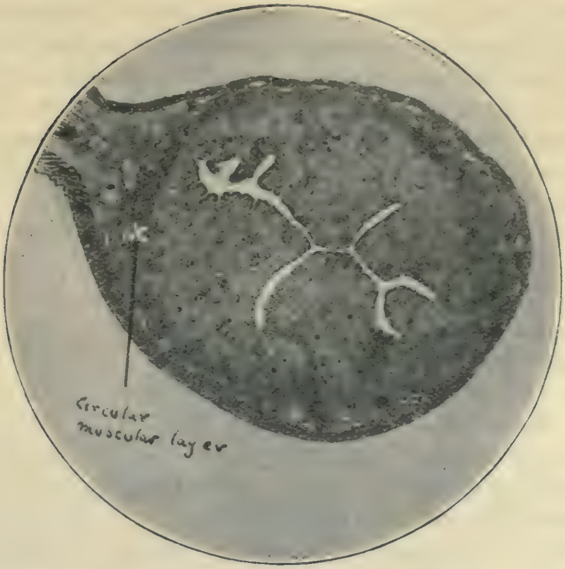

Fig. 90.—Transverse section through rabbit's uterus after ovariotomy, showing degenerative changes. (From Blair Bell, *British Medical Journal* and *Trans. Royal Society of Medicine.*)

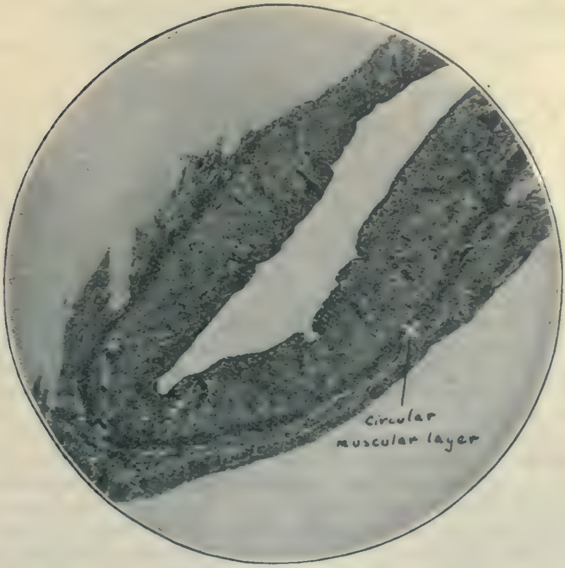

Fig. 91.—Transverse section through bitch's uterus 9½ months after ovariotomy. (From Blair Bell, *British Medical Journal* and *Trans. Royal Society of Medicine.*)

upon rabbits which confirmed those of Knauer, the ovaries being transplanted in various abnormal positions. Grigorieff also records two cases in which ovaries were successfully transplanted from one individual to another (heteroplastic transplantation). Ribbert found, in his experiments, that during the first month after transplantation the peripheral part of the grafted ovary remained unaltered, but the central part became transformed into connective tissue. At a later period, however, the central portion was again found to contain follicles. This fact is attributed to the conditions of increased nutrition which Ribbert supposed to prevail when the ovaries had been transplanted for a sufficiently long period to admit of their having acquired better vascular connections.

Halban[1] found that the uterus and mammary glands of guinea-pigs from which the ovaries had been removed shortly after birth, remained undeveloped; but, if the ovaries were removed from the normal position and grafted underneath the skin, the other generative organs developed normally.

Limon,[2] working upon rabbits, grafted ovaries beneath the muscle layers of the abdominal wall and on to the peritoneum of the same individuals. The follicles showed a tendency to degenerate, but the interstitial cells, after a short period of starvation, subsequently recuperated and acquired a condition of perfect vitality. Limon states that he found no sign of atrophy in the uterus after the transplantation of the ovaries to an abnormal position.

Carmichael[3] has recorded some success from experiments in which the ovaries of rabbits were transplanted on to abnormal positions in the same individuals (homoplastic transplantation), but there is no evidence in those cases that the grafted ovaries had any influence in preventing the degeneration of the uterus.

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[1] Halban, "Ueber den Einfluss der Ovarien auf die Entwickelung des Genitales," *Monatschr. f. Geburtsh. u. Gynäk.*, vol. xii.; 1900.

[2] Limon, "Observations sur l'État de la Glande Interstitielle dans les Ovaries Transplantés," *Jour. de Phys. et de Path. Gén.*, vol. xvi., 1904.

[3] Carmichael, "The Possibilities of Ovarian Grafting in the Human Subject, etc.," *Jour. of Obstet. and Gynæc.*, March 1907. Ovarian transplantation in different species of animals has also been carried out by Herlitzka ("Recherches sur la Transplantation des Ovaries," *Arch. Ital. de Biol.*, vol. xxxiv., 1900), Foà ("La Graffe des Ovaries en Relation avec Quelques Questions de Biologie," *Arch. Ital. de Biol.*, vol. xxxiv., 1900), Schultz ("Transplantation der Ovarien auf Männliche Tiere," *Central. f. All. Path. u. Path. Anat.*, vol. xi., 1900), Guthrie ("Successful Ovarian Transplantation in Fowls," *Internat. Congress of Phys.*, Heidelberg, 1907, Abstract in *Zent. f. Physiol.*, vol. xxi., 1907; "Further Results of Transplantation of Ovaries in Chickens," *Jour. of Exp. Zool.*, vol. v., 1908). Schultz and other investigators, without reference to the ovarian secretion theory, grafted the ovaries of guinea-pigs on to the bodies of males and recorded some success. Herlitzka also grafted the ovaries of guinea-pigs on to other individuals (heteroplastic transplantation), some females and some males. Only one experiment was at all successful, the ovary being transplanted on to a female. Foà was successful with several heteroplastic grafts in rabbits, and even succeeded in inducing pregnancy in an animal with a transplanted ovary. Guthrie's experiments were upon fowls. He states that the ova in the heteroplastically transplanted ovaries were influenced by the "foster-mother" (*i.e.* the birds into whom they were grafted), since the offspring produced by fertilising these ova partook of some of the foster-mother's characters (but see p. 209). For further references

The present writer also, working in conjunction with Dr. Jolly,[1] carried out a series of experiments upon rats in order to determine whether any histological changes occurred in the uterus after trans-

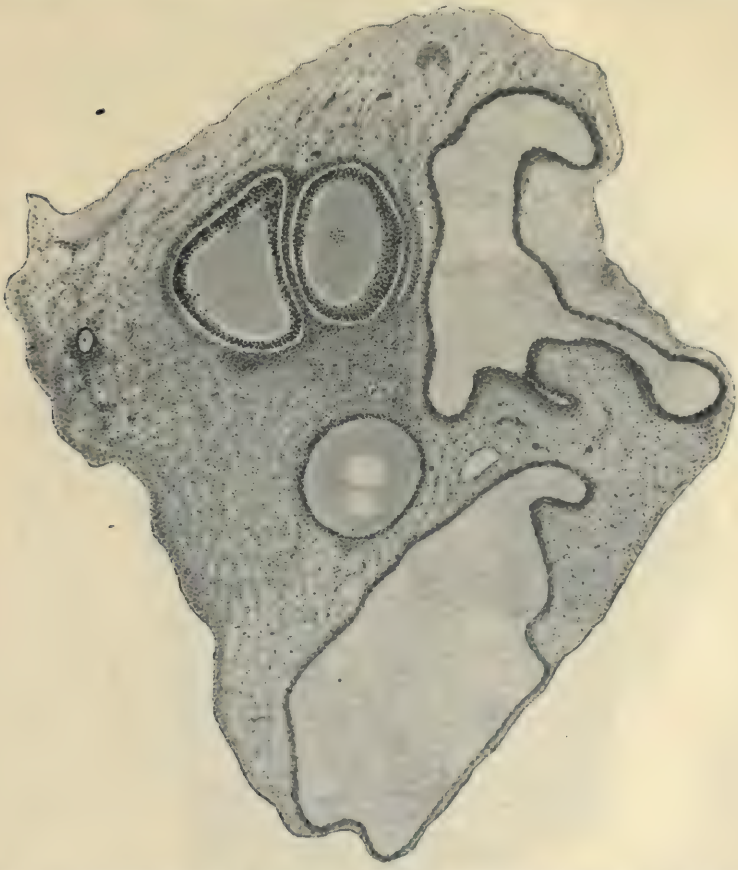

FIG. 92.—Section through ovary of rat after transplantation on to peritoneum, showing ovum, normal follicles, and follicles which have undergone cystic degeneration. (From Marshall and Jolly.)

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see Marshall and Jolly, "Results of Removal and Transplantation of Ovaries," *Trans. Roy. Soc. Edin.*, vol. xlv., 1907, and "Heteroplastic Transplantation, etc.," *Quar. Jour. Exp. Phys.*, vol. i., 1908; Sauvé, *Les Greffes Ovariennes*, Paris, 1909; Sand, *loc. cit.*, and Moore, *loc. cit.* Guthrie and Lee describe partially successful heteroplastic ovarian transplantation in dogs (*Jour. Amer. Med. Assoc.*, vol. lxiv., 1915). See also Minoura, p. 695, below.

[1] Marshall and Jolly, *loc. cit.*

planting the ovaries to new situations. Other experiments were undertaken in which the ovaries were simply removed without being transplanted. The rats were killed at intervals varying from one to fourteen months after the operation. In the control animals pronounced fibrosis or other atrophic appearances were always found in the uterus. On the other hand, in those animals in which ovaries had been successfully transplanted on to abnormal positions (such as on to the ventral peritoneum or into one of the kidneys) the uterus was found undegenerated. If, however, the ovarian graft failed to "take," or was only partially successful, the uterus presented

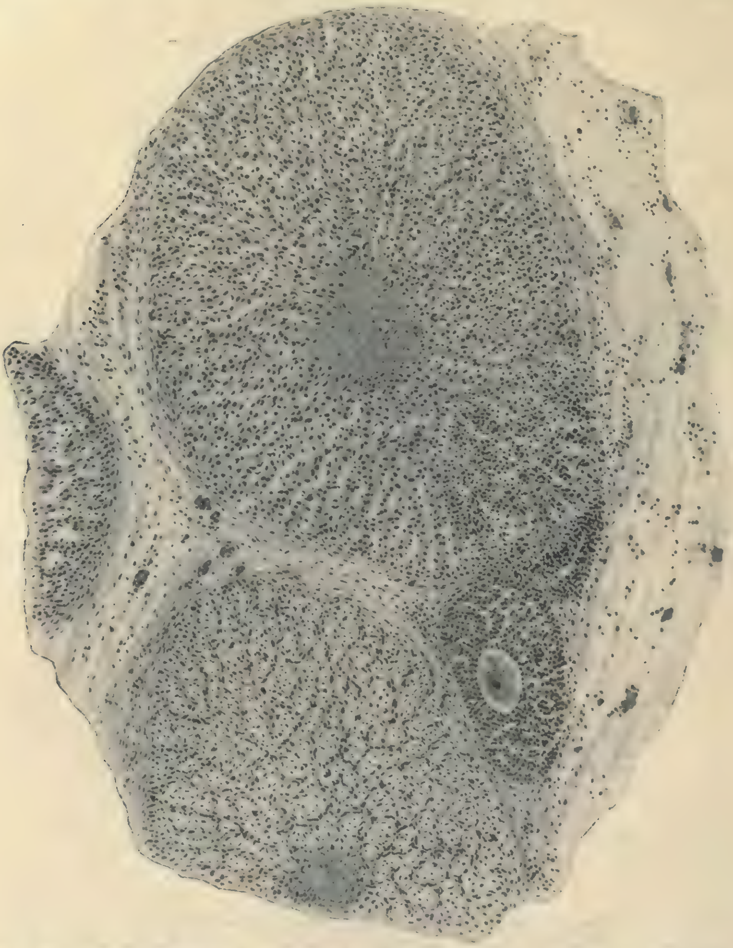

Fig. 93.—Section through ovary of rat after transplantation on to peritoneum, showing corpora lutea and small follicle with ovum. (From Marshall and Jolly.)

undoubted signs of degeneration. In the cases of transplantation from rat to rat, as in homoplastic transplantation, uterine degeneration was found to be arrested by a successful ovarian graft.

The successfully transplanted ovaries exhibited all the characteristic histological features of normal ovarian tissue, excepting that the germinal epithelium was invariably absorbed after the lapse of a short interval. In some cases a certain amount of degenerative change took place, only certain elements of the tissue being recognisable after the lapse of several months; thus, the stroma might present its normal appearance while the follicles had disappeared, or the greater part of the graft might be composed of luteal tissue alone. It was also observed that the successfully transplanted ovaries underwent the same cyclical changes as normal ovaries. Thus, in animals killed shortly before the commencement of the

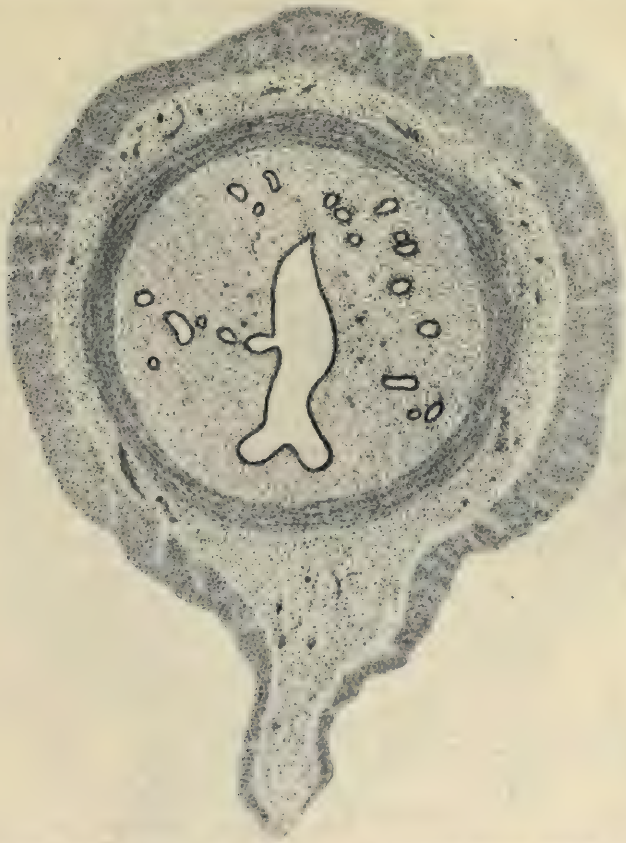

Fig. 94.—Transverse section through normal uterus of rat. (*Cf.* Figs. 95 and 96. From Marshall and Jolly.)

breeding season, large follicles were found in the grafts, while at a later period corpora lutea were present, showing that ovulation had occurred in the transplanted ovaries. In one case, a homoplastic graft was found to be normal after fourteen months, while a normal heteroplastic graft was composed entirely of healthy ovarian tissue (with follicles and ova) after six months. In these experiments the ovaries were grafted into the substance of the kidneys.

Homoplastic transplantation was found to be more easily accomplished than heteroplastic transplantation. This result could hardly be ascribed to increased difficulties in the performance of the latter operation, since the technique was identical in each case. Furthermore, our successes in heteroplastic transplantation were usually obtained in experiments in which two rats from the same litter were known to have been employed, so that the ovaries were grafted into whole sisters, but we were not sure of the relationship in every case.

These experiments clearly indicate that the nature of the ovarian influence is chemical rather than nervous, since the successfully grafted ovaries, while still maintaining their functions, had lost their normal nervous connections. It is probable, therefore, that the uterus depends for its proper nutrition upon substances secreted by the ovaries.

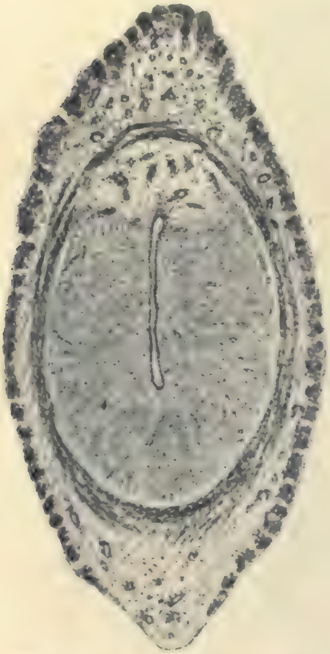

Fig. 95.—Transverse section through uterus of rat after ovariotomy, showing degenerative changes.

(*Cf.* Figs. 94 and 96. From Marshall and Jolly.)

Further evidence in support of the view that the ovary produces an internal secretion is provided by the results of ovarian medication or the administration of preparations of ovarian substance for medicinal purposes. It is somewhat difficult, however, to know precisely what value to assign to this practice about which medical authorities still appear to differ. Brown-Séquard[1] seems to have been the first to employ ovarian extracts medicinally. He supposed them to produce similar effects to those brought about by testicular extracts, but they did not appear to be so powerful. Since Brown-Séquard's time ovarian preparations have been used medicinally in a large number of cases with more or less successful results. The fresh ovaries are themselves taken, or ovarian tissue is given in the form of

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[1] Brown-Séquard, "Des Effets produits chez l'Homme par des Injections, etc," *C. R. de la Soc. de Biol.*, 1889.

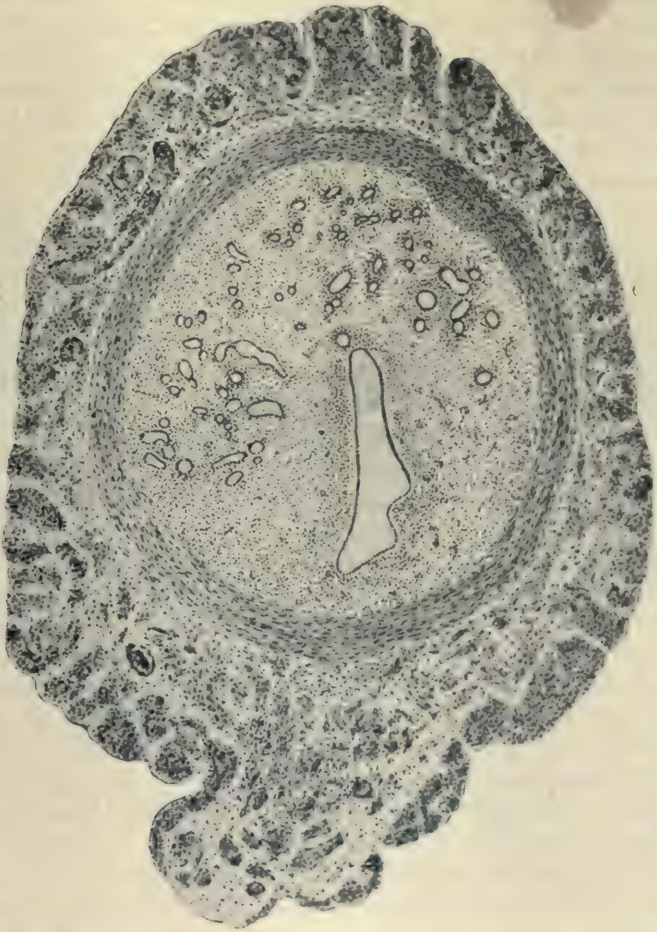

FIG. 96.—Transverse section through uterus of rat after ovarian transplantation. The uterus is normal.

(See text and *cf.* Figs. 94 and 95. From Marshall and Jolly.)

fluid or powder (ovarine, oöphorine, ovigenine, etc.). The fresh ovaries or ovarian powder are eaten, but the fluid can be administered either by the mouth, by the rectum, or by hypodermic injection. These methods of treatment are said to have met with considerable success in cases of amenorrhœa, chlorosis, and menopause troubles, both natural and post-operative. Some physicians, however, report only a very moderate or doubtful success, while a few state that the results are nearly always unsatisfactory.[1] The method of administering the extract by the mouth is open to the criticism that the "active principle" of the ovarian secretion may be altered in the metabolic processes of digestion. Moreover, it is by no means certain that the "active principle" may not be destroyed in the manufacture of the preparations. Again, it is not unlikely that the effects of ovarian medication may depend, not only upon the method of preparing the extracts, but also upon the condition of the ovaries from which the extracts are made, and it would seem unreasonable to expect to obtain uniform results from the indiscriminate usage of ovaries in different stages of cyclical activity (*e.g.* ovaries with prominent follicles like those from animals "on heat," or ovaries with corpora lutea like those of pregnant animals, or ovaries in a state of relative quiescence like those of anœstrous animals). Nevertheless ovarian medication frequently in conjunction with the usage of other gland extracts (mammary gland or thyroid) continues to be practised, and in many instances valuable results are said to be obtained.

The effects are discussed at some length in a memoir by Bestion de Camboulas,[2] who describes a large number of experiments upon dogs, rabbits, and guinea-pigs, as well as a series of clinical observations. Experiments were performed on male animals as well as on female ones. The lethal injection of ovarian extract was found to be about twice as much in non-pregnant females as in males or pregnant females. With non-toxic doses the females gained weight, but the males lost weight. The lesions discovered after lethal doses were congestion of the viscera, and minute hæmorrhages in the dorsal and lumbar regions of the spinal cord. Bestion also administered ovarian extract to his patients, and states that he obtained distinctly beneficial results. Menopause troubles are described as either disappearing altogether or becoming much ameliorated, while rapid improvement was observed in cases of chlorosis and amenorrhœa. Bestion says that ovarian extract should never be administered to pregnant women, since it causes such grave results when given to pregnant animals.

Jentzner and Beuttner[3] found that the subcutaneous injection of ovarian extract in castrated animals did not supply the place of living ovarian substance, and Mr. Carmichael and the present writer[4] experienced a similar result after making a series of intra-peritoneal injections of commercial extract, the uterine atrophy which followed ovariotomy being in no degree diminished.

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[1] For references to the literature of ovarian medication, see Andrews, "Internal Secretion of the Ovary," *Jour. of Obstet. and Gyn.*, vol. v., 1904.

[2] Bestion de Camboulas, *Le Suc Ovarien*, Paris, 1898.

[3] Jentzner and Beuttner, "Experimentelle Untersuchungen zur Frage der Castrationsatrophie," *Zeitsch. f. Geburtsh. u. Gynäk.*, vol. xlii., 1900.

[4] Carmichael and Marshall, *loc. cit.*

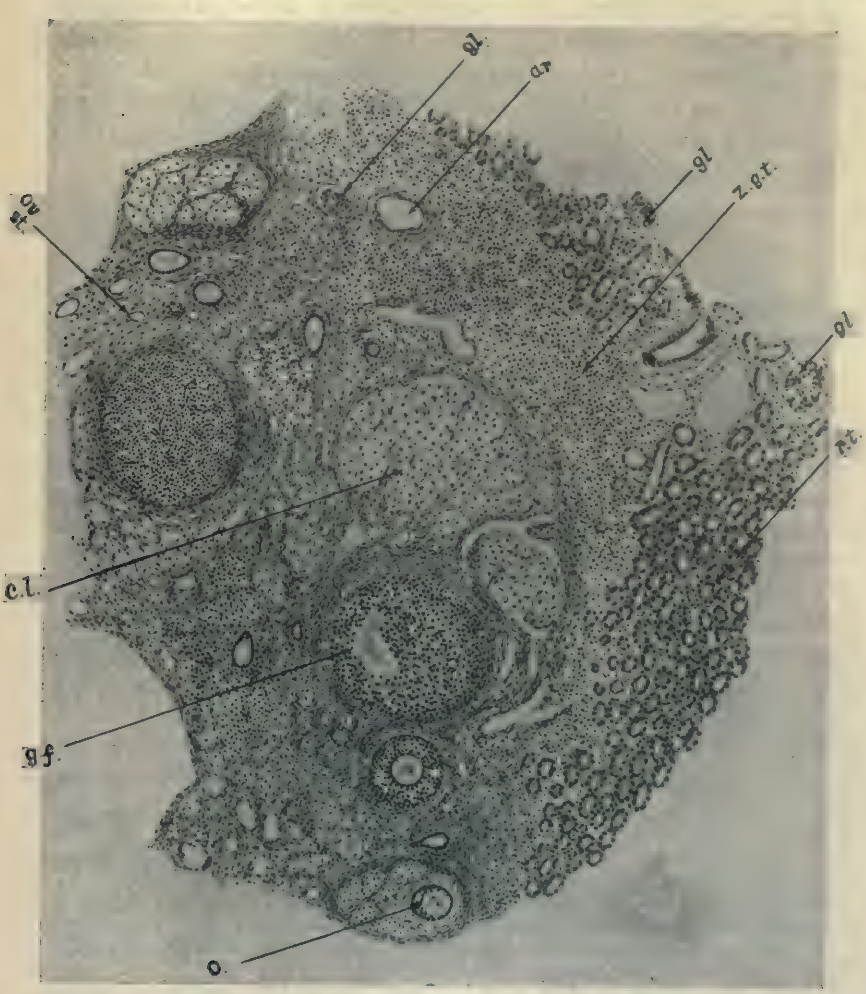

Fig. 96A.—Section through rat's kidney, into the tissue of which an ovary had been transplanted. (From Marshall and Jolly, *Quar. Jour. of Experimental Physiology*.)

ar, Artery; *c.l.*, corpus luteum; *g.f.*, Graafian follicle; *gl.*, glomerulus of kidney; *ov.st.*, ovarian stroma; *r.t.*, renal tubule; *z.g.t.*, zone of granulation tissue between ovarian tissue and tissue of kidney.

It has been shown that the ovary possesses considerable capacity for regenerating tissue after partial removal, and also that if one ovary is extirpated the remaining one may undergo an apparent increase in size, which is probably of the nature of a compensatory hypertrophy. These facts may perhaps be regarded as supplying some further evidence that the ovary is an organ of internal secretion[1] (*cf.* the testis, p. 338). Lipschutz,[2] however, while confirming the above recorded observations, states that the augmentation in the ovarian volume is due to the growth and increase of the follicles.

According to Loisel,[3] the ovary fulfils a purifying function in the organism, and absorbs injurious products. This theory seems to have little experimental basis.[4]

THE FACTORS WHICH DETERMINE THE OCCURRENCE OF HEAT AND MENSTRUATION

Pflüger[5] advanced the theory that menstruation is brought about by a nervous reflex, owing its origin to the pressure of the growing Graafian follicles upon the nerve endings in the ovary. This view received some support from Strassmann,[6] who claimed to have induced "heat" in animals by injecting gelatine into their ovaries, and so producing intra-ovarian pressure. Elizabeth Winterhalter's[7] alleged discovery of a sympathetic ganglion in the ovary also tended to support this theory; but von Herff[8] discredited her description, which, so far, has received no confirmation.

Goltz[9] showed that heat in animals is not brought about by a cerebral or spinal reflex. In one experiment the spinal cord of a bitch was transected in the lumbar region; normal prœstrum, followed by œstrus and conception, occurred as usual, but copulation was unaccompanied by sensation, though the animal showed a marked inclination towards the dog. In another experiment the lumbar part of the spinal cord was completely removed without interfering with the cyclical recurrence of prœstrum and œstrus. Moreover,

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[1] Carmichael and Marshall, "On the Occurrence of Compensatory Hypertrophy in the Ovary," *Jour. of Physiol.*, vol. xxxvi., 1908.

[2] Lipschutz, Wagner, and Tamen, "Sur l'Hypertrophie des Fragments Ovariens dans la Castration Partielle," *C. R. de la Soc. de Biol.*, vol. lxxxvi., 1922.

[3] Loisel, "Les Poisons des Glandes génitales," *C. R. de la Soc. de Biol.*, vol. lv., 1903; vol. lvi., 1904; and vol. lvii., 1904.

[4] Ovariotomy has an effect on the skeleton comparable to that of castration. See Shattock and Seligman, "The Influence of Oophorectomy upon the Growth of the Pelvis," *Proc. Roy. Soc. Med.*, Path. Sec., 1910.

[5] Pflüger, *Über die Bedeutung und Ursache der Menstruation*, Berlin, 1865.

[6] Strassmann, *Lehrbuch der gerichtlichen Medizin*, 1895.

[7] Winterhalter, "Ein Sympathisches Ganglion im Menschlichen Ovarium," *Arch. f. Gynäk.*, vol. li., 1896.

[8] Von Herff, "Giebt es ein Sympathisches Ganglion im Menschlichen Ovarium," *Arch. f. Gynäk.*, vol. li., 1896. For information upon the innervation of the ovary, see von Herff, "Über den feineren Verlauf der Nerven im Eierstock," *Zeitsch. f. Geb. u. Gynäk.*, vol. xxiv., 1893.

[9] Goltz, "Ueber den Einfluss des Nervensystems auf die Vorgänge während der Schwangerschaft und des Gebärakts," *Pflüger's Arch.*, vol. ix., 1874. Goltz and Ewald, "Der Hund mit verkürztem Rückenmark," *Pflüger's Arch.*, vol. lxiii., 1896.

Sherrington,[1] after transecting the spinal cord of a bitch in the cervical region, and headwards of the connection between the sympathetic system and the cord, observed that heat of normal duration and character continued to recur in the animal so operated upon. The case, described by Brachet,[2] of a woman suffering from paraplegia in the lower part of the body and legs, but who conceived and became pregnant, may also be cited.

There are other facts which indicate that menstruation is not caused by a nervous reflex set up by ovulation or by the pressure of the growing follicles. Gynæcologists have pointed out that in the human subject ovulation and menstruation are not necessarily associated, and Heape[3] has shown that the ovaries of menstruating monkeys do not always contain follicles in a state approaching ripeness.

But whereas the evidence is clear that heat and menstruation are not brought about by nervous reflexes arising from the ovary, it is equally obvious that these processes are dependent upon some ovarian influence. For, if the ovaries are removed, heat and menstruation no longer take place.

Some authors, however, have denied this, and cases have been cited of the occurrence of menstruation after surgical ovariotomy. For example, three cases have recently been described by Doran,[4] in each of which the two ovaries were believed to have been removed, although menstruation recurred at irregular intervals after the operation. Further cases have lately been reported by Blair Bell[5] and other writers. It seems probable that these exceptional cases are to be explained on the supposition that the extirpation of ovarian substance was not quite complete, and that the tissue which remained behind underwent hypertrophy subsequently to the operation. That this is the true interpretation is rendered the more probable in view of the cases referred to by Gordon,[6] Doran,[7] Meredith,[8] and others, in which pregnancy occurred after the supposed removal of both ovaries (see also p. 370). Doran[9] also records a large series of cases in which menstruation entirely ceased after ovariotomy.[1]

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[1] Sherrington, *The Integrative Action of the Nervous System*, London, 1906.

[2] Brachet, *Recherches*, 2nd Edition, Paris, 1837.

[3] Heape, "The Menstruation and Ovulation of *Macacus rhesus*," *Phil. Trans.*, B., vol. clxxxviii., 1897.

[4] Doran, "Sub-total Hysterectomy for Fibroids," *Lancet*, Part II., November 1905.

[5] Blair Bell, "Preliminary Note on a New Theory of Female Generative Activity," *Liverpool Medico-Chirurgical Journal*, July 1906.

[6] Gordon, "Two Pregnancies following the Removal of both Tubes and Ovaries," *Trans. Amer. Gynæc. Soc.*, vol. xxi., 1896.

[7] Doran, "Pregnancy after the Removal of both Ovaries," *Jour. Obstet. and Gynæc.*, vol. ii., 1902.

[8] Meredith, "Pregnancy after Removal of both Ovaries," *Brit. Med. Jour.*, Part I., 1904.

[9] Doran, "Sub-total Hysterectomy for Fibroids," *Lancet*, Part II., Nov. 1905.

Morris[2] gives an account of a woman aged twenty, who suffered from amenorrhœa, her uterus being infantile. He states that he transplanted on to her fundus uteri an ovary which he obtained from another woman, aged thirty. The transplantation is said to have been successful, inducing menstruation after two months. In another case Morris[3] states that he transplanted an ovary into a woman whose own ovaries had been previously removed, and that the graft was so far successful that conception, followed by a normal pregnancy, occurred as a result. It has been suggested, however, that in this case a portion of the woman's original ovary may have been left behind, and that this accounted for the pregnancy (*cf.* p. 359). Glass[4] describes a case of a patient who was suffering from menopause troubles due to the extirpation of the ovaries. After the transplantation of an ovary from another woman had been effected, the patient was gradually restored to health and menstruation was renewed. Dudley[5] mentions a case in which a double pyosalpinx was removed, and the right ovary implanted on the fundus uteri. The patient menstruated regularly afterwards. Again, in a case recorded by Cramer of Bonn,[6] the ovary of a woman suffering from osteomalacia was extirpated and transplanted into a second woman whose genital organs were much atrophied. As a result of the graft the genital organs of the woman in whom the ovary was transplanted became normal, menstruation started once more, and the breasts secreted colostrum. In none of these cases, however, is there any record of post-mortem evidence showing that the transplanted ovaries had become successfully attached.

Halban[7] states that he found in monkeys that, whereas menstruation ceased after double ovariotomy, it recurred again after ovarian transplantation, even though the ovary was grafted in a position different from the normal one.

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[1] The continuance of menstruation after the removal of two ovaries may be due to the presence of accessory ovaries which are occasionally known to exist. Oliver says that ovariotomy, even when the ovaries are removed with a portion of the broad ligament, does not necessarily stop menstruation ("On the Question of an Internal Secretion from the Human Ovary," *Jour. of Physiol.*, vol. xliv., 1912).

[2] Morris, "The Ovarian Graft," *New York Med. Jour.*, 1895.

[3] Morris, "A Case of Heteroplastic Ovarian Grafting followed by Pregnancy, etc.," *New York Med. Jour.*, vol. lxix., 1906.

[4] Glass, "An Experiment in Transplantation of the Entire Human Ovary," *Medical News*, 1899.

[5] Dudley, "Über Intra-uterine Implantation des Ovariums," *Internat. Gyn. Congress*, Amsterdam, 1899.

[6] Cramer (H.), "Transplantation menschlicher Ovarien," *München. med. Wochenschr.*, 1906.

[7] Halban, "Über den Einfluss der Ovarien auf die Entwickelung des Genitales," *Sitz.-Ber. Akad. Wissenschaft*, Wien, vol. cx., 1901.

Those cases already referred to, in which atrophy of the uterus took place after the removal of the ovaries, also indicate the dependence of the menstrual and prooestrous functions upon the presence of ovarian tissue, since normal heat could not occur if the uterus were in a condition of fibrotic degeneration, while certain of Knauer's experiments[1] afford evidence that heat can be experienced by animals in which the ovaries are transplanted to abnormal positions.

Veterinarians are generally agreed that heat does not occur in dogs whose ovaries have been extirpated. Moreover, ovariotomy is sometimes practised on mares in order to prevent œstrus, and so suppress the vicious symptoms which are liable to render the animals periodically unworkable.[2]

The spaying of sows is a well-known commercial practice, and if properly carried out prevents the recurrence of "heat." The ordinary method is to make an incision in the side and withdraw the uterus along with the ovaries, but sometimes one or both ovaries are left behind, and the sows come "in use." This has led to the discrediting of the practice, the importance of removing the minute ovaries (the pigs being only about seven weeks old) not being properly appreciated.[3]

Dr. Jolly and the author[4] have shown, further, that normal prooestrum, followed by œstrus, can occur in dogs which only possess transplanted ovaries, thus confirming the observations of Knauer and Halban. In the experiments in question the animals' own ovaries were removed, and a few weeks later the ovaries obtained from other dogs were grafted in abnormal positions (*e.g.* between the abdominal muscular layers or on the ventral border of the peritoneal cavity). The grafts seem to have become attached, and to have survived for a sufficiently long period to exercise an influence over the generative system; but they eventually underwent considerable fibrous degeneration, as the post-mortem evidence afterwards showed.

As a result of these experiments it may probably be concluded that the enhanced activity which the ovaries exhibit during the final stages of follicular development is accompanied by metabolic changes which result in an increase in the production of the ovarian secretion, and that this phenomenon is the main factor in the periodic recurrence of heat and menstruation.[1] It has been observed that not only are the internal and external generative organs affected at these periods, but there is also a distinct hypertrophy of the breasts, and this, as Miss Lane-Claypon and Starling[2] have pointed out, is probably due also to an increase in the ovarian metabolism.[3]

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[1] Knauer, *loc. cit.*

[2] Hobday, "Ovariotomy of Troublesome Mares," *Veterinary Jour.*, New Series, vol. xiii., April 1906.

[3] Mackenzie and Marshall, "Ovariotomy in Sows, etc.," *Jour. of Agric. Science*, vol. v., 1913. See below, p. 389.

[4] Marshall and Jolly, "Contributions to the Physiology of Mammalian Reproduction: Part II. The Ovary as an Organ of Internal Secretion," *Phil. Trans.*, B., vol. cxcviii., 1905.

There is a certain amount of direct evidence that heat and menstruation are brought about by an internal secretion elaborated by the ovaries. It has been found that the injection of fresh ovarian extract obtained from animals which are "on heat" may appear to produce in anœstrous animals a transient congestion of the external generative organs resembling that of the normal proœstrous condition, but similar slight indications have been observed at other times irrespectively of any injections.[4] Miss Lane-Claypon and Starling also have described congestion in the uterus after the injection of ovarian extract; but, in their experiments, the ovaries employed were those of pregnant animals. Moreover, Aschner[5] has described uterine hæmorrhage after injection of ovarian extracts.

Further evidence that the proœstrous and œstrous conditions are produced by substances circulating in the blood, but not necessarily elaborated in the ovaries, is supplied by certain facts recorded by Halban.[6] This author affirms that the milk of suckling sows is affected during the periods of heat, in consequence of which the young are liable to develop unhealthy symptoms. In a similar way the milk of women is said to be affected during menstruation. Moreover, according to Youatt,[7] cows can be brought "on heat" artificially by feeding them on milk supplied from other cows which are in that condition.

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[1] As already pointed out, menstruation and ovulation are not necessarily associated. It is probable, however, that the ovarian metabolism is increased at the menstrual periods, although there may not always be any follicles present in a sufficiently mature condition to admit of ovulation occurring in the œstrous periods which normally follow them.

[2] Lane-Claypon and Starling, "An Experimental Inquiry into the Factors which Determine the Growth and Activity of the Mammary Glands," *Proc. Roy. Soc.*, B., vol. lxxvii., 1906.

[3] According to Pearl and Surface ("The Nature of the Stimulus which causes a Shell to be formed on a Bird's Egg," *Science*, New Series, vol. xxix., 1909), the stimulus which excites the activity of the shell-secreting glands in the fowl's oviduct is mechanical, being brought about by a strictly local reflex. The shape of the egg is determined by the muscular activity of the cells of the oviduct (Pearl, "Studies on the Physiology of Reproduction in the Domestic Fowl: I. Regulation in the Morphogenetic Activity of the Oviduct," *Jour. of Exp. Zool.*, vol. vi., 1909).

[4] Marshall and Jolly, *loc. cit.*

[5] Aschner, "Ueber brunstartige Erscheinungen (Hyperämia und Hämorrhagia am weiblichen Genitale) nach subkutaner Injektion von Ovarial- und Plazentaextrakt," *Arch. f. Gynäk.*, vol. xcix., 1913. *Cf.* Iscovesco, *C. R. de Soc. de Biol.*, vol. lxxiii., 1912.

[6] Halban, *loc. cit.*

[7] Youatt, *Cattle*, London, 1835.

Heape[1] has suggested that heat may be due to a "generative ferment" which he supposes to be periodically present in the blood. At the same time he is of opinion that a hypothetical substance called "gonadin," which is secreted by the generative glands, is also an essential factor. The precise relation in which gonadin and the generative ferment were supposed to stand to one another is not very clear.

Assuming that heat and menstruation are brought about, either directly or indirectly, through a stimulus depending upon the secretory activity of the ovary, it is still an open question as to what part of the organ is concerned in the process. Fraenkel[2] has supposed that the secretion in question is supplied by the corpus luteum. This conclusion is based upon nine cases in which the corpus luteum was destroyed by the cautery, and in eight of which the next menstrual period was missed. In the remaining case it is supposed that the secretion responsible for producing menstruation had already been formed in sufficient quantity and passed into the circulation at the time of the cauterisation. Fraenkel's theory, however, is disproved by the fact that ovulation in most Mammals does not occur until œstrus, or, at any rate, until the end of the proœstrum (see p. 131), and consequently corpora lutea are not present in the ovaries (for the corpora lutea dating from one œstrus do not always persist until the next œstrus, which may be many months afterwards). Heape's observations[3] on the absence of corpora lutea in menstruating monkeys may be again cited in this connection. Moreover, Ries[4] has reported a case of a woman with whom menstruation occurred normally after an operation in which an oozing corpus luteum, which was a source of hæmorrhage in the peritoneal cavity, had been peeled out. It should be mentioned that Fraenkel's views on menstruation are part of a general theory which is discussed more fully below (p. 368).

Seeing that the corpus luteum is not responsible for inducing menstruation, it becomes necessary to conclude that either the follicular epithelial cells or the interstitial cells of the ovarian stroma (or both of these) are concerned in bringing about the process (see p. 119).

Some experiments by Mr. Runciman and the author[5] on bitches point to the conclusion that the presence of mature follicles is not essential for the recurrence of heat. All the follicles approaching ripeness were ruptured artificially by pricking three weeks and two months before heat periods were due. In both cases heat appeared at about the normal time. The inference was that the process of follicular maturation and the phenomena of heat are both effects of some further factor which must be sought for in the ovaries elsewhere than in the ripe Graafian follicle. As Robinson points out, interstitial tissue may be found in the bitch's ovaries, but according to O'Donoghue[1] it is not always present in the ovaries of Mammals. Robinson[2] expresses the view that the cells of the ruptured follicles were not necessarily functionally interfered with, notwithstanding the fact that they later developed into cells resembling those of corpora lutea. He states further that in ferrets œstrus only occurs when the ovaries contain follicles of a certain degree of development, and that such follicles are present as long as œstrus persists. This particular stage of development he calls the preinseminal stage when the follicles "appear to take on the function of providing the secretion which is responsible for the phenomena of proœstrum and œstrus."[3]

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[1] Heape, "Ovulation and Degeneration of Ova in the Rabbit," *Proc. Roy. Soc.*, B., vol. lxxvi., 1905.

[2] Fraenkel, "Die Function des Corpus Luteum," *Arch. f. Gynäk.*, vol. lxviii., 1903.

[3] Heape, "The Menstruation and Ovulation of *Macacus rhesus*," *Phil. Trans.*, B., clxxxviii., 1897.

[4] Ries, "A Contribution to the Function of the Corpus Luteum," *Amer. Jour. Obstet.*, vol. xlix., 1904.

[5] Marshall and Runciman, "On the Ovarian Factor concerned in the Recurrence of the Œstrous Cycle," *Jour. of Physiol.*, vol. xlix., 1914.

It has already been shown that the breeding season, and consequently the recurrence of the œstrous cycle, are controlled to a great extent by the general environmental conditions, since these affect the physical state of the body (Chapters I. and II.). This is particularly well seen in certain of the domestic animals, in which "heat" may be caused to recur more frequently by the supply of special kinds of stimulating foods (p. 635). It would appear, therefore, that the metabolic activity of the ovaries is increased by these methods, and that the problematical internal secretion is elaborated in greater quantity.

Lastly, it must not be forgotten that, whereas it is exceedingly probable that the proœstrous changes of the uterus are brought about by a specific excitant or hormone[4] arising in the ovaries, little or nothing is known concerning the chain of causation leading to that disturbed state of the nervous metabolism, the existence of which during œstrus is so plainly manifested in the display of sexual feeling.

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[1] O'Donoghue, "On the Corpora Lutea and the Interstitial Tissue in the Ovary and in Marsupialia," *Quar. Jour. Micr. Science*, vol. lxvi., 1916.

[2] Robinson, "The Formation, etc., of Ovarian Follicles in Ferrets," *Trans. Roy. Soc. Edin.*, vol. lii., 1918.

[3] For further information see Bucura, "Zur Theorie der inneren Sekretion des Eierstocks," *Zent. für Gyn.*, 1913.

[4] Starling has proposed the term hormone (from the Greek, ὁρμαω, I excite or arouse) for such internal secretions or excitants of a chemical nature. Thus, secretin, or the internal secretion of the duodenum, which excites pancreatic secretion, is a hormone. See Starling, "The Chemical Correlation of the Functions of the Body," Croonian Lectures, London, 1905 ; also Lane-Claypon and Starling, *loc. cit.*

THE FUNCTION OF THE CORPUS LUTEUM

Various theories have been put forward to explain the formation and presence of the corpus luteum. According to one view, which was taught until recently, the development of this structure was merely a result of the excessive vascularisation which characterises the entire internal generative tract during the period of pregnancy. Very little consideration of the actual facts is needed to convince one of the inadequacy of this explanation. The blood supply to the generative organs is greatest during the later stages of pregnancy, when the corpus luteum is becoming diminished in size. Moreover, the rapid hypertrophy of the luteal cells takes place independently of pregnancy during the very early stages of development at a time when there is no appreciable congestion of the genital organs. According to another theory, the corpus luteum was of the nature of a stop-gap, whose purpose was to preserve the cortical circulation of the ovary by preventing an excessive formation of scar-tissue.[1]

Prenant[2] seems to have been the first to suggest that the corpus luteum was a ductless gland. He supposed it to produce an internal secretion which exercised an influence over the general metabolism in the manner attributed to the internal ovarian secretion. The phenomenon of chlorosis was explained as being due to the absence of this secretion. Prenant supposed also that the corpus luteum had the further function of preventing ovulation during pregnancy or between the œstrous periods.

This theory was supported by Regaud and Policard,[3] who stated that, by means of special methods of staining, droplets of a secretory substance could be detected in the cells of the corpus luteum of the hedgehog.

Beard[4] independently suggested that the corpus luteum is a contrivance to suppress ovulation during pregnancy, while he supposed it to degenerate before parturition in order to admit of ovulation occurring immediately afterwards. It must be pointed out, however, that in many Mammals, if not in the majority, the breeding season does not recur until after an anœstrous period, which is often of considerable duration, and that it is extremely improbable that ovulation occurs during this period.

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[1] Clark, "Ursprung, Wachstum, und Ende des Corpus Luteum," *Arch. f. Anat. u. Phys.*, Anat. Abth., 1898. Whitridge Williams, *Obstetrics*, New York, 1903.

[2] Prenant, "La Valeur Morphologique du Corps Jaune," *Rev. Gén. des Sciences*, 1898.

[3] Regaud and Policard, "Fonction Glandulaire de l'Epithelium Ovarique chez la Chienne," *C. R. de Soc. de Biol.*, vol. liii., 1901.

[4] Beard, *The Span of Gestation and the Cause of Birth*, Jena, 1897.

Beard's theory has been adopted by Sandes,[1] who investigated the corpus luteum of the marsupial cat (*Dasyurus viverrinus*, see p. 142). This author states that in *Dasyurus*, as in most other Mammals, the corpus luteum disappears towards the end of the lactation period, when the next œstrus is approaching, and the follicles are beginning to grow in preparation for the ensuing ovulation. He says, further, that as soon as the corpus luteum is formed, the ova in the surrounding follicles, which were up to that time in various stages of active development, begin to undergo atrophy. This atrophy commences in the follicles in closest proximity to the newly formed corpus luteum, and is continued in the surrounding follicles in ever-widening circles. Sandes suggests that this result is brought about by mechanical pressure, or is due to the internal secretion of the corpus luteum, if it has one. Without in any way disputing the accuracy of the facts which Sandes describes, it is difficult to understand what advantage is gained by a mechanism having a not more important object than that of securing the degeneration of the surplus ova within the ovary instead of externally to it, and it is not easy to see how, according to the usually accepted doctrines of utility and natural selection, an organ having such a purposeless function could ever have been developed at all.[2]

Gustav Born was the first to suggest that the function of the corpus luteum might be to provide an internal secretion which assisted in the attachment of the embryo to the uterine mucosa. Unable to undertake the investigation himself, he persuaded Ludwig Fraenkel[3] to put his theory to an experimental test. For this purpose a series of experiments upon rabbits was proceeded with, the ovaries being removed at intervals varying from one to six days after the occurrence of coition, the period of gestation in this animal being thirty days. The rabbits were afterwards killed, when it was found that the extirpation of the ovaries had prevented the fixation of the embryos, or had caused these to be aborted. In other cases the corpora lutea are described as having been burnt out by the electric cautery without destroying the rest of the ovaries, and these experiments led to a similar result. Control experiments were performed by removing one ovary while leaving the other, and by destroying some of the corpora lutea but not all, and in the majority of these cases the animals produced young. The experiments resulted, therefore, in supporting the view that there is an intimate connection between the presence of the corpus luteum and the occurrence of pregnancy, and that this connection is in a certain sense one of cause and effect.

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[1] Sandes, "The Corpus Luteum of *Dasyurus viverrinus*," *Proc. Linnean Soc.*, New South Wales, vol. xxviii., 1903.

[2] Pearl and Surface state that extract of corpus luteum of cow injected into a laying fowl inhibits ovulation. ("Studies on the Physiology of Reproduction in the Domestic Fowl," IX., *Jour. Biol. Chem.*, vol. xix., 1914.)

[3] Fraenkel and Cohn, "Experimentelle Untersuchungen über den Einfluss des Corpus Luteum auf die Insertion des Eies," *Anat. Anz.*, vol. xx., 1901; Fraenkel, *loc. cit.*

Apart from the experimental evidence, Fraenkel adduces certain other facts which tend to support the theory that the corpus luteum is an organ of internal secretion. He points out that its general structure is eminently suggestive of its being a ductless gland, since it is formed mainly of large epitheloid cells surrounded by a network of capillaries and arranged in regular rows or columns not unlike those of the cortex of the supra-renal body. Moreover, the increase in the size of the corpus luteum, until it becomes larger than a Graafian follicle, seems inexplicable on any other view. This unusual capacity for growth is clearly out of all proportion to that of the rest of the ovary, and it is pointed out, further, that when the corpus luteum is most hyperæmic, the other part of the ovary is unusually anæmic, while towards the end of pregnancy, when the increase in the blood supply to the generative organs is at its height, the corpus luteum is often reduced to little more than a scar. Fraenkel also lays some stress on the discovery that the luteal cells are derived from the follicular epithelium and not from the connective tissue of the stroma. Furthermore, he observes that whereas many cases have been recorded in which double ovariotomy was performed during pregnancy without interfering with the further course of development, in none of these, so far as he is aware, was the operation conducted in the early weeks.

Fraenkel observes also that in non-placental Mammals (Marsupials and Monotremes) the corpus luteum is rudimentary or does not exist at all. Sandes,[1] who has carefully described the formation of the corpus luteum in the marsupial cat, points out that this is erroneous, and says that there is a large corpus luteum in the members of both these groups. It should be remembered, however, that in Marsupials the embryo is nourished by a "yolk-sac placenta," while in at least one genus (*Perameles*) a definite allantoic placenta exists. In Monotremes there is a pronounced hypertrophy of the follicular epithelium following upon ovulation, but the corpus luteum is not normal in this group, since there appears to be no ingrowth of connective tissue or blood-vessels from the follicular wall (see p. 143).

A similar objection, that might be raised in opposition to Fraenkel's hypothesis, is that structures resembling corpora lutea have been found in the ovaries of certain of the lower Vertebrates (see p. 145). This resemblance relates chiefly to the hypertrophy of the cells of the follicular epithelium after the discharge of the ova. Such an objection is not to be regarded as a serious one, for there is nothing improbable in the supposition that rudimentary corpora lutea, providing probably some sort of secretion, should have been developed before the acquirement of the function, which, according to Fraenkel's hypothesis, is possessed by the fully formed structure which characterises the placental Mammalia.

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[1] Sandes, *loc. cit.*

Fraenkel has also pointed out, as an argument in favour of his theory, that in ectopic or extra-uterine pregnancy the uterus undergoes the usual changes although there is no ovum in the uterine cavity. It is clear, therefore, that the changes do not occur simply as a consequence of the presence of the ovum. It is also pointed out that in normal pregnancy the uterine changes commence before the ovum enters the uterus.

Again, the theory that the corpus luteum is responsible for the attachment and early development of the embryo receives some support from those cases in which pathological conditions in the embryo have been found associated with pathological conditions in the corpus luteum.[1] Thus lutein cysts are frequently found in apparent correlation with chorionepitheliomata.

Fraenkel's general conclusions regarding the functions of the corpus luteum may be summarised as follows: The corpus luteum is a ductless gland which is renewed every four weeks during reproductive life in the human female, and at different intervals in the various lower Mammals. Strictly speaking, there is only one corpus luteum which represents the ovarian organ of internal secretion, and is regenerated periodically in slightly different positions in the ovaries. Its function is to control the nutrition of the uterus from puberty until the menopause, to prevent it from lapsing into the infantile condition or undergoing atrophy, and to prepare its mucous membrane for the maintenance of the ovum. If the ovum be fertilised, the corpus luteum is responsible for maintaining the raised nutrition of the uterus during the first part of gestation. If the ovum be unfertilised it merely produces the hyperæmia of menstruation, and then undergoes degeneration until it is renewed in a fresh position. Since the corpus luteum is, *par excellence*, *the* ovarian gland, "lutein" or the extract of this organ, and not preparations of the entire ovary, should be employed for the purposes of ovarian medication.

Reasons have already been given for concluding that this extended theory of the meaning and function of the corpus luteum is untenable (p. 363). The fact that in a very large number of animals, heat, and presumably, therefore, ovulation, occur at infrequent intervals does not support it, while it has been shown that, in some animals at any rate, ovulation does not take place until œstrus, and consequently that at the time of the procœstrous hyperæmia there are no corpora lutea present in the ovary. These facts, however, are in no way opposed to that part of Fraenkel's theory which assigns to the corpus luteum the function of governing the fixation of the ovum and helping to maintain its nutrition during the first stages of pregnancy.

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[1] *Cf.* Malcolm Campbell, "Pathological Condition of the Ovaries as a Possible Factor in the Etiology of Uterine Fibroids," *Scottish Med. and Surg. Jour.*, vol. xvi., 1905.

Dr. Jolly and the author[1] have carried out a series of experiments upon dogs and rats in which the ovaries were extirpated at different stages during pregnancy, as in Fraenkel's experiments upon rabbits. In the experiments on dogs, ovariotomy was performed at intervals ranging from three days to four weeks after impregnation. The pregnancy was discontinued in every case excepting one, in which a portion of the right ovary which contained the degenerate remains of two undoubted corpora lutea were found post mortem, three days after parturition, when the dog was killed. In this experiment ovariotomy was performed three days after copulation, and parturition occurred fifty days subsequently. Only a single pup was produced, and birth was premature. The pup died after being suckled normally for three days. The ovaries were also removed from a large number of rats, most of which were in early stages of pregnancy. Pregnancy was continued in no case in which ovariotomy was performed during the first six days. In other cases, in which the ovaries were removed at periods varying from the sixth day until near the end of pregnancy, the young were produced normally at full time.[2] Control experiments were also carried out in which the abdominal cavity was opened up during an early stage of pregnancy and the ovaries were cauterised, or in which one ovary was removed and not the other, and in these experiments the course of pregnancy was not interfered with.[3] We purposely refrained from attempting to extirpate the corpora lutea only while leaving the rest of the ovary, as it appeared to us to be practically impossible to destroy the whole of the luteal tissue without injuring the entire organ. The ovaries during pregnancy consist very largely of corpora lutea, and any attempt in a relatively small animal to discriminate between luteal tissue and stroma, while the ovary was lying in its normal position in the body cavity, seemed in our judgment to be impracticable.

It will be seen that our experiments on the results of ovariotomy during pregnancy fully confirm those of Fraenkel. It must be pointed out, however, that there is no evidence that the corpus luteum governs the fixation of the embryo in any other than the indirect sense implied in the supposition that the secretion elaborated by that organ acts as a stimulus which excites the uterine mucosa to undergo the necessary hypertrophy. In this general sense, also, it is probably true that the luteal secretion (or, at any rate, the secretion of the ovary) assists in nourishing the embryo during the first stages of pregnancy, since there is every reason for concluding that it helps to maintain the raised nutrition of the uterus. It has been shown that the presence of the ovaries is not essential for the continuance of pregnancy in the later stages, when the corpora lutea are in process of degeneration. It would seem not unlikely, therefore, that the atrophic changes (fibrosis) which take place in the decidua serotina, or maternal placenta, in the later part of the gestation period are directly correlated with the degeneration of the corpus luteum.[1]

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[1] Marshall and Jolly, *loc. cit.*

[2] In our paper the period of gestation in the rat was wrongly stated to be twenty-eight days. It is in reality about twenty-one days.

[3] *Cf.* Carmichael and Marshall, *loc. cit.*

Cases have been recorded by Essen-Möller,[2] Graefe,[3] and Flatau,[4] in which pregnancy was not interrupted by double ovariotomy in women when performed in the early stages of pregnancy. These cases are undoubtedly very exceptional, and it seems legitimate to conclude that a small portion of an ovary, probably containing luteal tissue, was left behind accidentally at the time of the operation. So able and experienced an operator as Bland Sutton[5] has recently testified to the extraordinary difficulty experienced in removing the whole of the ovarian tissue in ovariotomy, and the distinguished French obstetrician, Lucas-Championnière,[6] has expressed himself in the same sense, so that there is nothing unreasonable in the assumption that the operation of removal is sometimes incomplete when performed on pregnant women.

Daels[7] has recorded a large series of experiments upon guinea-pigs and rats in which he found that bilateral castration invariably interrupted the course of pregnancy during rather more than the first half of its duration. In control experiments portions of mesentery or other tissue, or only one ovary instead of both, were extirpated, and in these cases the pregnancy was continued. Furthermore, Kleinhaus and Schenk[1] found that destruction of the corpora lutea of rabbits, after the ninth day of gestation, did not necessarily produce abortion, but that the same operation at an earlier period invariably brought the gestation to a premature end.

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[1] It has been suggested that the corpus luteum contributes an essential factor in the nourishment of the embryo through the trophoblast, and that it consequently ceases to be functional in the later part of pregnancy when the trophoblast is superseded by the allantoic placenta. See Andrews, *loc. cit.*

[2] Essen-Möller, "Doppelseitige Ovariotomie im Anfange der Schwangerschaft," *Central. f. Gynäk.*, vol. xxviii., 1904.

[3] Graefe, "Zur Ovariotomie in der Schwangerschaft," *Zeitsch. f. Geb. u. Gynak.*, vol. lvi., 1905.

[4] Flatau, "Ueber Ovariotomie während der Schwangerschaft," *Arch. f. Gynäk*, vol. lxxxii., 1907.

[5] Bland Sutton, "A Clinical Lecture on the Value and Fate of Belated Ovaries," *Medical Press*, vol. cxxxv., (31st July) 1907.

[6] Lucas-Championnière, "Sur une Observation de Graffe Ovarienne Suivie de Grossesse," *Jour. de Méd. et de Chirurgie Pratiques*, vol. lxxviii., (May) 1907.

[7] Daels, "On the Relations between the Ovaries and the Uterus," *Surgery, Gynecology and Obstetrics*, vol. vi., 1908.

Ancel[2] and Bouin have shown in a succession of papers that the rabbit's uterus undergoes growth, vascularisation and muscular hypertrophy after ovulation, although the ova are not fertilised (*e.g.* owing to coition having been sterile through the vasa deferentia of the male having been cut). There is a great glandular hypertrophy of the uterine mucous membrane and active secretion takes place. These changes are succeeded by regression, when the blood-vessels break down and corpuscles are extravasated in the stroma and the glands become smaller. The regression sets in about the thirteenth day, or after a period nearly equal to half the duration of pregnancy. The corpus luteum begins to retrogress about the same time. There is, therefore, a close parallelism between the growth and regression of the corpus luteum and a series of cyclical changes which take place in the uterus. Ancel and Bouin have shown further that there is a parallelism between the development of the corpus luteum and the growth of the mammary gland in the rabbit (see below, Chapter XIII.). In the absence of corpora lutea neither the uterine growth nor the mammary growth take place.

Although doubt has been expressed by some authors[3] as to the existence of the correlation it has now been abundantly established by several independent investigators working on different animals. O'Donoghue[4] has confirmed the results for the rabbit's mammary gland. The development of the mammary tissue in the later part of pregnancy has been ascribed by Ancel and Bouin to the influence of the myometrial gland (see below, p. 618), but Hammond[1] has shown that it is far more likely to be due to the continued influence of the corpora lutea, depending upon the presence of the fœtus, since these organs do not attain the same dimensions under the experimental condition (which may be called pseudo-pregnancy, a condition not normally occurring in the rabbit, which usually only has corpora lutea associated with pregnancy, since it does not ovulate without copulation). According to Hammond, the corpora lutea do not degenerate in the later part of pregnancy, and consequently the corpora lutea of pseudo-pregnancy in the rabbit are comparable to the corpora lutea spuria of most other Mammals, although it would seem probable that, when produced, they persist for a longer time and exert a greater influence than the "false" corpora lutea of those polyœstrous animals which ovulate spontaneously. Milk may be expressed from the glands towards the end of the pseudo-pregnant period even in rabbits which have only copulated once, having previously been virgins. The uterine hypertrophy occurring under the influence of the corpus luteum formed after sterile coition has been shown to be very pronounced in the rabbit, while the blood extravasation towards the end of pseudo-pregnancy is also marked[2] (see above, p. 101).

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[1] Kleinhaus and Schenk, "Experimentales zur Frage nach der Funktion des Corpus Luteum," *Zeitsch. f. Geb. u. Gynäk.*, vol. lxi., 1907.

[2] Ancel and Bouin, "Sur la Fonction des Corps jaunes," *C. R. de la Soc. de Biol.*, vol. lxvi., 1909; "Le Développement de la Glande Mammaire pendant la Gestation est determiné par le Corps jaune," *C. R. de la Soc. de Biol.*, vol. lxvii., 1909; "Sur les Fonctions du Corp Jaune Gestatif," *Jour. Phys. et Path. Gen.*, vols. xii. and xiii., 1910 and 1911. (For myometrical gland see also *C. R. de la Soc. de Biol.*, vol. lxxii., 1912; and *C. R. Acad. Sci.*, vol. cliv., 1912; and see below, Chapter XIII., for further account and references.)

[3] Dubreuil and Regaud, "Sur les Relations fonctionelles des Corps jaunes avec l'Uterus non gravidé," I., II., III., and IV., *C. R. de la Soc. de Biol.*, vol. lxvii., 1909. See also earlier papers in vol. lxv., 1908, and vol. lxvi., 1909. Niskoubina, on the other hand, tends to confirm Ancel and Bouin, "Recherches expérimentales sur la Fonction des Corps jaunes," *C. R. de la Soc. de Biol.*, vol. lxvi., 1909.

[4] O'Donoghue, "The Artificial Production of Corpora Lutea," *Proc. Phys. Soc.*, *Jour. of Physiol.*, vol. xlvi., 1913.

Lastly, it has been found that rabbits which had been pseudo-pregnant will pluck their breasts and prepare a nest for young although there were none to be born (see below, p. 576).

In the marsupial cat (*Dasyurus*) there is only one kind of corpus luteum[3] (that of pregnancy or pseudo-pregnancy), and the changes which occur in the mammary glands as a result of luteal influence are identical irrespectively of whether gestation occurs or not. The uterine changes are in a general way similar to those occurring under artificial pseudo-pregnancy in the rabbit.[4]

Leo Loeb[5] has shown that in the non-pregnant guinea-pig there is a definite cycle for the mammary gland and that it corresponds with the ovarian and uterine cycles. The gland tissue proliferates when a new ovulation is imminent and to a greater extent later in the cycle as a result probably of the cumulative influence of the corpora lutea. Extirpation of the corpora lutea was followed (see below, p. 620, Chapter XIII.) by an arresting effect, and by an acceleration of the next ovulation.[1] As long as the corpora functionate the presence of mature follicles does not produce those uterine changes which are characteristic of heat.

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[1] Hammond, "On the Causes Responsible for the Developmental Progress of the Mammary Glands, etc.," *Proc. Roy. Soc.*, B., vol. lxxxix., 1916.

[2] Hammond and Marshall, "The Functional Correlation between the Ovaries, Uterus, and Mammary Glands," *Proc. Roy. Soc.*, B., vol. lxxxvii., 1914.

[3] Hill and O'Donoghue, "The Reproductive Cycle in the Marsupial *Dasyurus*," *Quar. Jour. Micr. Science*, vol. lix., 1913.

[4] Retterer and Voronoff (*C. R. de la Soc. de Biol.*, vol. lxxxiv., 1921) record growth of uterine glands and cotyledons in goats and sheep through an ovarian graft containing a corpus luteum and after previous ovariotomy.

[5] Loeb and Hesselberg, "The Cyclic Changes in the Mammary Gland under Normal and Pathological Conditions," *Jour. of Exp. Med.*, vol. xxv., 1917; see also *Biol. Bull.*, vol. xxvii., 1914.

In polyœstrous animals the corpus luteum spurium usually degenerates after a short period so as to make way for the maturation of new follicles and the process of ovulation at the frequently recurring œstrous periods. Otherwise the ripening follicles degenerate under the influence of the corpus luteum. Thus follicular atrophy occurs in widening circles around the corpus luteum of *Dasyurus.* The more rapid degeneration of the corpus luteum spurium has probably taken place in association with the acquirement of the polyœstrous habit since it would be detrimental to fecundity if these structures persisted for as long a time as the corpora lutea of pregnancy.

In monœstrous animals, on the other hand, the persistence of the corpus luteum spurium over a period equal to that of pregnancy would not tend towards infecundity, and this probably accounts for the condition found in the dog.[2] Keller[3] was the first to describe the post-œstrous hyperplasia in the uterine glands and the retrogressive stage which follows, observations which have since been confirmed and extended. The epithelium of the glands, after being first columnar afterwards becomes cubical, and in the retrogressive stage the lumina contain a colloid and sometimes desquamated cells. There is much hæmorrhage in the stroma. Retrogression sets in about thirty days after ovulation, the mammary glands going through a similar cycle, growth being followed by a secretion of fluid which may be identical with milk. These changes occur in correlation with the growth and degeneration of corpora lutea (see above, Chapter III., p. 99).

The corpus luteum in polyœstrous animals is known sometimes to persist for an abnormal length of time, and according to Williams may be a cause of long-continued sterility. Why the organ should persist is not clear, but Williams[4] states that this condition occurs most frequently in young cows or heifers which have suffered some time previously from contagious granular vaginitis. In certain cows œstrus is said to take place in spite of there being a corpus luteum present, but when this is so the periods are shortened to twelve or fifteen hours instead of the normal duration which is said to be double that time, and the cows if served in this condition fail to conceive. It is probable that in spite of œstrus taking place ovulation fails to occur. The continuance of the corpus luteum as an apparent result of vaginitis or venereal disease may be due to the irritation of the generative organs, and is perhaps comparable to the normal stimulus set up by pregnancy, which results in the persistence of the corpus luteum in polyœstrous as in monœstrous animals, or to the mechanical and artificial stimuli induced by Leo Loeb in the uterus of the guinea-pig, which is followed not only by the formation of decidual cells at the place where irritation is experienced, but by the persistence of the luteal bodies in the ovary.

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[1] Excision of corpora lutea in pregnancy, while promoting ovulation, is not followed by a new uterine cycle, as during pregnancy a mechanism is at work preventing the uterus from responding to stimuli given off by the ovary (Loeb).

[2] Marshall and Halnan, "On the Post-Œstrous Changes occurring in Generative Organs and Mammary Glands of the Non-Pregnant Dog," *Proc. Roy. Soc.*, B., vol. lxxxix., 1917.

[3] Keller, "Ueber den Bau des Endometrium beim Hunde," *Anat. Hefte*, vol. cxviii., 1909.

[4] Williams (W. L.), *Veterinary Obstetrics*, New York, 1917.

Williams states that sterility as a result of the persistent corpus luteum can be remedied by squeezing out this organ from the ovary, the operation being performed through the rectum or vagina, and that œstrus recurs within a short time of the corpus luteum being eliminated. According to the clinical records of the New York State Veterinary College, at Cornell University ninety-five per cent. of the cattle so treated conceived at the first subsequent service. Albrechtsen,[1] however, throws some doubt on the practical value of this method of treatment. Hess,[2] on the other hand, records a number of observations and experiments which are confirmatory of those of Williams.

According to Loeb,[3] deciduomata (*i.e.* nodules having the structure of decidua) can be produced experimentally in the uterine mucosa of the guinea-pig by making a number of transverse and longitudinal cuts so as to break the continuity of the tissue. The nodules originate through a proliferation of the interglandular connective tissue. Loeb states further that this can only happen during a certain definite period after the occurrence of copulation or heat. The changes cannot be induced on the first day after heat, nor after the tenth day, but deciduomata are readily formed between the third or fourth and eighth or ninth days. The uterus is therefore most responsive when freshly formed corpora lutea are present in the ovaries and therefore at a different time from that at which the proliferating effect on the mammary gland is produced (see pp. 619

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[1] Albrechtsen, *The Sterility of Cows*, English Translation, Chicago, 1917.

[2] Hess, *Die Sterilität des Rindes, ihre Erkennung und Behandlung*, Hannover, 1921. *Cf.* also Oppermann, *Sterilität der Haustiere*, Hannover, 1922.

[3] Loeb (L.), "The Production of Deciduomata, and the Relation between the Ovaries and the Formation of the Decidua," *Jour. Amer. Med. Assoc.*, vol. l., (6th June) 1908; *Medical Record*, vol. lxxvii., (25th June) 1910; *Arch. für Entwick.-Mech.*, vol. xxxii., 1911; *Surgery, Obstetrics, and Gynecology*, vol. xxv., 1917; and *Jour. Exp. Med.*, vol. xxv., 1917.

and 620). The changes were not excited by the presence of ova in the uterus, since they took place when the lower part of that organ was ligatured off so as to prevent the passage of the ova. On the other hand, if the ovaries were extirpated deciduomata could not be produced. If the corpora lutea were as far as possible burnt out of the ovaries by the electric cautery, deciduomata were not generally produced; but owing to the difficulty of properly performing these experiments, the results were not quite conclusive. Lastly, when pieces of uterus were transplanted into the subcutaneous tissue, deciduomata were formed in the grafted pieces. It is concluded, therefore, that the ovaries at certain periods after ovulation (and probably the corpora lutea) elaborate a predisposing substance in the presence of which indifferent stimuli (traumatisms) may produce deciduomata. Hammond has obtained similar results with rabbits.[1]

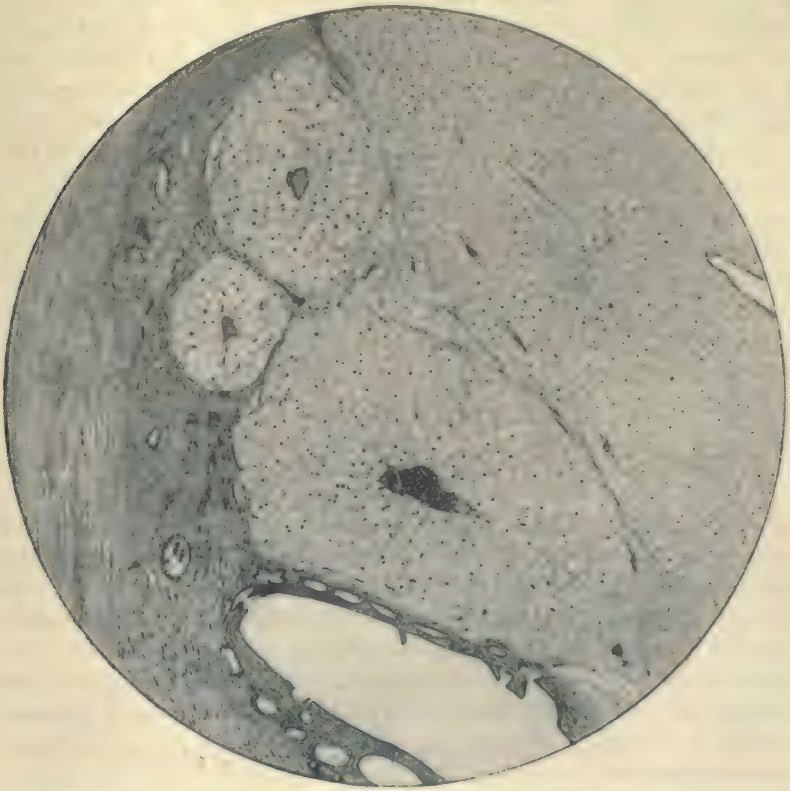

FIG. 97.—Experimentally produced placenta of pseudo-pregnant rabbit; section of uterus showing connective tissue forming decidual cells which enclose vessels. (From Hammond.)

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[1] Hammond, *loc. cit.*

It has been shown that the uterine mucosa undergoes atrophy after the complete removal of the ovaries, and it seems hardly probable that this process can be arrested by the presence of a fertilised ovum in the early stages of pregnancy. On the other hand, it is scarcely conceivable that an ovum could become attached to a uterine mucous membrane which was in process of degenerating. It would appear, however, that in the latter half or two-thirds of pregnancy, when the uterus has already undergone great hypertrophy, the presence of the ovaries may be dispensed with.[1] Furthermore, it has just been mentioned that the maternal placenta undergoes a partial degeneration in the later stages of embryonic development.

Miss Lane-Claypon[2] has shown that the interstitial cells of the ovarian stroma undergo an increase in size during the period of gestation, but this increase is not so great as that of the luteal cells. Consequently, she suggests that these cells also may produce a secretion of the nature postulated for the cells of the corpus luteum. If this is so, the circumstance that the interstitial cells do not hypertrophy to the same extent as the luteal cells may perhaps be ascribed to the different conditions of mechanical pressure existing in the ovarian stroma.

The Supposed Internal Secretion of the Uterus

Although the bulk of evidence obtained clinically points to the conclusion that the uterine functions fall into abeyance after the extirpation of the ovaries, while the relatively few exceptions to this rule are probably to be explained on the supposition of incomplete removal, some surgeons and gynæcologists have adopted the view that the uterus is capable of functional activity independently of the ovaries. A few writers have even gone further, and have affirmed the belief that the ovarian functions themselves are dependent upon uterine influence.

Zweifel and Abel,[3] in describing the after-histories of cases of hysterectomy, stated that, in their experience, when the whole of the uterus was removed, entire atrophy of the ovaries always followed, so that menopause symptoms set in similar to those occurring after ovariotomy. In those cases, however, in which a portion of the uterine mucous membrane was conserved, menstruation continued and there were no menopause symptoms. Consequently, these surgeons have advocated the operation of sub-total hysterectomy wherever possible in preference to complete removal, believing that the functional activity of the ovary is in some way dependent on the presence of the uterus.

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[1] It has yet to be proved, however, that the further course of development is absolutely normal after ovariotomy in the later part of pregnancy.

[2] Lane-Claypon, "On the Origin and Life-History of the Interstitial Cells of the Ovary of the Rabbit," *Proc. Roy. Soc.*, B., vol. lxxvii., 1905.

[3] Zweifel, Deutsche Gesellschaft für Gynäkologie in Berlin, *Zentral. f. Gynäk.*, No. 21, 1899. Abel, "Dauererfolge der Zweifelschen Myomektomie," *Arch. f. Gynäk.*, vol. lvii., 1899.

Doran,[1] in tracing the after-histories of sixty cases of sub-total hysterectomy, is disposed to concur with Zweifel and Abel in advising that the uterus should be removed above the cervix. In support of this contention he cites two cases in which menstruation persisted after the removal of the body of the uterus, the cervix being left behind. In a later paper[2] he mentions four cases in which both ovaries were removed and the menopause was neither immediate nor complete. He records forty additional cases of sub-total hysterectomy, with after-histories, making a hundred in all.

Mandl and Bürger,[3] in a monograph dealing with the subject, express the belief that in those cases in which the ovaries are conserved after hysterectomy there is a gradual cessation of function on the part of these organs, resulting from their degeneration.

Holzbach,[4] on the other hand, states that as a rule the ovaries do not atrophy after hysterectomy, and that, when such degeneration does occur, it is probably due to interference with the nervous connections consequent upon the operation of removal.

Graves[5] states that after hysterectomy vasomotor disturbances ensue with approximately equal frequency whether the ovaries be retained *in situ*, totally oblated, or transplanted. Retention of ovarian tissue after removal of the uterus is said to be of little or no physiological value and may even be productive of serious trouble to the patient owing to the formation of cysts or adhesions.

Blair Bell[6] once suggested that menstruation was brought about by an internal secretion of the uterus, while he supposed ovulation to depend on the circulation of this secretion, which he called "uterine."

Bond[7] has put forward the view that the ovarian secretion is influenced by a saline secretion from the anœstrous uterus, the two, however, acting antagonistically to one another, so that the prevention of the uterine secretion by hysterectomy favours the hypertrophy of the ovaries. Bond's view, therefore, is diametrically opposed to that formerly held by Blair Bell.

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[1] Doran, "Sub-total Hysterectomy for Fibroids," *Lancet*, Part II., November 1905.

[2] Doran, "Sub-total Hysterectomy for Fibromyoma Uteri," *Proc. Roy. Soc. Med.*, (February) 1911; *Lancet*, vol. clxxx., (14th Jan.) 1911.

[3] Mandl and Bürger, *Die Biologische Bedeutung der Eierstöcke nach Entfernung der Gebärmutter*, Leipzig, 1904.

[4] Holzbach, "Ueber die Function der nach Totalextirpation des Uterus zurückgelassenen Ovarien," *Arch. f. Gynäk.*, vol. lxxx., 1906.

[5] Graves, "Retention of Ovarian Tissue after Hysterectomy," *Surg., Gynec. and Obstet.*, vol. xxv., 1917.

[6] Blair Bell, *loc. cit.* But *cf. The Sex Complex*, London, 1916.

[7] Bond, "Some Points in Uterine and Ovarian Physiology and Pathology in Rabbits," *Brit. Med. Jour.*, Part II., July 1906.

Bond records two experiments on the results of hysterectomy in rabbits. In one the entire uterus was removed and the animal killed after five months. Both ovaries were found to be normal. In the other experiment the left uterine cornu only was extirpated, and the rabbit was killed after five months. In this case also the ovaries showed no signs of degeneration. As a result of these experiments Bond affirms that the prevention of the saline secretion of the uterine mucosa by previous hysterectomy favours the overgrowth of luteal tissue in the ovary.

Stress has been laid by various writers upon the well-known fact that whereas the corpora lutea of the ovary continue to grow for a considerable period of time if pregnancy supervenes after ovulation, this hypertrophy soon ceases in the absence of pregnancy. Bond records an experiment upon a rabbit in which one of the ovaries, after transplantation in an abnormal position, was found to contain a somewhat aberrant "corpus luteum of pregnancy" in association with a gravid uterus. Such observations are regarded by him as supplying evidence of an internal uterine secretion acting on the ovaries and so exciting a growth of luteal tissue. This secretion is supposed by Bond to be quite different from the saline fluid elaborated by the anœstrous uterus.[1] It must be remembered, however, that pregnancy produces a profound influence over the entire organism, and not merely over the ovaries; also that, as recorded above, corpora lutea are formed habitually in the rabbit's ovaries after sterile coition and develop during a pseudo-pregnant period.

Certain other authors, such as Loewenthal,[2] have suggested theories which imply a dependence on the part of the ovaries upon some function of the uterus; but, excepting for the two experiments of Bond referred to above, and a series of experiments undertaken by the author in collaboration with Mr. Carmichael,[3] no systematic investigation ever appears to have been attempted until very recently upon the effects of hysterectomy.

In our experiments we removed the uterus, either entirely or leaving only the cervix, from a number of very young immature rabbits. The animals were killed after they had become fully grown—in some cases not until ten months after the operation. In every experiment the ovaries were found to have developed normally. In some cases, also, copulation was observed on the rabbits being put with the buck. Many of the ovaries contained typical corpora lutea, showing that ovulation had taken place. Also in four experiments on fully grown rats hysterectomy was performed, and the animals were killed several months subsequently. The ovaries in no instance showed any indications of atrophy. On the other hand, marked uterine degeneration was observed in rats after the removal of the ovaries for shorter periods of time.[1]

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[1] Bond, "Certain Undescribed Features in the Secretory Activity of the Uterus and Fallopian Tubes," *Jour. Physiol.*, vol. xxii., 1898.

[2] Loewenthal, "Eine neue Deutung des Menstruationprocess," *Arch. f. Gynäk.*, vol. xxiv., 1884.

[3] Carmichael and Marshall, *Proc. Roy. Soc.*, *loc. cit.*

As a result of these experiments, it may be concluded that the growth and development of the ovaries is in no way dependent upon the presence of the uterus. Such a conclusion is no doubt opposed by some of the clinical evidence, but it is one which was to be expected on phylogenetic grounds, since the uterus is an organ which came into existence comparatively recently in the course of vertebrate evolution, whereas the ovary is common to all Metazoa. It is possible, in those surgical cases in which the ovaries underwent atrophy after the removal of the uterus, that this was due to vascular interference.[2]

THE CORRELATION BETWEEN THE GENERATIVE ORGANS AND THE DUCTLESS GLANDS[3]

The Thymus.—Noel Paton[4] and Henderson[5] have stated that there is a reciprocal relation between the thymus and the testis, each checking the growth of the other. This conclusion is based on a series of observations on cattle and guinea-pigs. In the former it was found that castration delayed the onset of the atrophy of the thymus, for the average weight of that organ in bulls up to three and a quarter years old was considerably less than that in oxen. In guinea-pigs Paton states that in those animals in which the thymus was removed at a time prior to the normal period of atrophy for that organ, there was an increase in the growth of the testis. On the other hand, Soli[1] states that extirpation of the thymus, carried out in young rabbits, guinea-pigs, and fowls, caused inhibition of testicular development, and sometimes even complete arrest of growth by that organ.

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[1] Marshall and Jolly, "Results of Removal and Transplantation of Ovaries," *Trans. Roy. Soc. Edin.*, vol. xlv., 1907.

[2] Boston has recorded four cases of women where the uterus was congenitally absent, but in whom the development of the breasts and other changes relating to puberty excepting menstruation were experienced. Sentiment, sexual desire, and sexual sensation are stated to have been normal in each case ("Absence of the Uterus in Three Sisters and Two Cousins," *Lancet*, Part I., January 1907). It may also be mentioned that Sellheim found that removal of the oviducts in pheasants does not result in a shrivelling up of the ovaries and the assumption of secondary male characters as has been stated (*Zeitsch. f. Gynäk.*, 1904, No. 24). It has not been determined whether the generative organs (apart from the uterus) undergo the characteristic prooestrous changes after hysterectomy, since these changes are comparatively slight and difficult to detect in rabbits.

[3] For a symposium on the relation of the organs of internal secretion to obstetrics and gynæcology, see *Surgery, Obstetrics and Gynecology*, vol. xxv., September 1917. See also Blair Bell, *The Sex Complex*, London, 1916.

[4] Paton, "The Relationship of the Thymus to the Sexual Organs," *Jour. of Physiol.*, vol. xxxii., 1904.

[5] Henderson, "On the Relationship of the Thymus to the Sexual Organs," *Jour. of Physiol.*, vol. xxxi., 1904.

Lucien and Parisot[2] also found some arrest in the growth of the testes after thymectomy in the rabbit. Klose and Vogt,[3] who worked on dogs, reported hyperplasia of the testes followed by atrophic changes. They also describe thymectomy as producing a softening of the bones or a retardation of the growth of the bony tissues, besides other pathological phenomena. Similar changes are recorded by Matti,[4] who was, however, unable to find any relation between thymectomy and the time of spermatogenesis. Pappenheimer,[5] working upon rats, obtained no evidence of thymectomy having any effect upon spermatogenesis or the weight of the testes.

As a result of a further series of experiments Paton[6] concluded that the thymus and testes do not act antagonistically to one another, but that each organ has a stimulating effect upon growth, the one organ compensating for the removal of the other by undergoing hypertrophy, whereas neither castration nor thymectomy alone had any influence upon growth. The double operation upon young guinea-pigs checked growth.

Mr. Halnan and the present writer,[7] in a series of experiments upon guinea-pigs, while confirming the castration effect upon the thymus, failed to obtain evidence of the thymectomy effect either upon growth or upon the testes; we found further that simultaneous removal of the testes and thymus did not influence growth. Our results, as well as those of Paton, were analysed by Udny Yule, who concluded that Paton's thymectomy results may have been due to chance variation.

According to Hewer[8] it is possible to induce a hyperthymic condition in young rats by feeding them upon extract or upon the fresh gland. Miss Hewer states further that cessation of spermatogenesis or testicular atrophy is an accompaniment of this condition. Moreover, irradiation of the thymus region with X-rays is said to be followed by degenerative changes in the testes, and irradiation of the gonads by the appearance of Hassal's corpuscles and other hypertrophic changes in the thymus. The data do not, however, appear to have been large enough or definite enough to warrant the deduction of precise conclusions.

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[1] Soli, "Contribution à la Connaissance de la Formation du Thymus chez le Poulet et chez quelques Mammifères," *Arch. Ital. de Biol.*, vol. lxii., 1909.

[2] Lucien and Parisot, "Variation ponderale consécutive a la Thymectomie chez le Lapin," *C. R. de la Soc. de Biol.*, vol. lxv., 1918.

[3] Klose and Vogt, "Klinik und Biologie der Thymusdrüse," *Beitr. z. kl. Chir.*, vol. xcii., 1910.

[4] Matti, "Untersuchung ueber die Wirkung experimentellen Ausshaltung d. Thymusdruse," *Grenzgeb. d. Med. u. Chir.*, vol. xxiv., 1912.

[5] Pappenheimer, "The Thymus Gland, etc., and the Female Genital Tract," *Surg., Obstet. and Gyn.*, vol. xxv., 1916. This paper contains many references.

[6] Paton, "The Thymus and Sexual Organs," *Jour. of Physiol.*, vol. xlii., 1911.

[7] Halnan and Marshall, "On the Relation between the Thymus and Generative Organs, etc.," with a Note by Udny Yule, *Proc. Roy. Soc.*, B., vol. lxxxviii., 1914.

[8] Hewer, "The Effect of Thymus Feeding, etc.," *Jour. of Physiol.*, vol. xlvii., 1914; "The Direct and Indirect Effect of X-Rays on the Thymus Gland and Reproductive Organs," *Jour. of Physiol.*, vol. l., 1916.

On the other hand, there can be no doubt about the effect of early castration upon the thymus, the involution of which is markedly delayed as shown by Calzolari,[1] Ranzi and Tandler,[2] Gellin,[3] Klose and Vogt,[4] Manassini,[5] and Squadrini,[6] as well as the investigators already referred to.

Valtorti[7] obtained similar results from ovariotomy in young rabbits, but he also claimed that thymectomy is followed by degenerative changes in the ovary. The last results would seem uncertain in view of the frequency of follicular degeneration in rabbits' ovaries under normal conditions.

Gudernatsch[8] states that tadpoles fed upon thymus extract grew to an enormous size and postponed undergoing metamorphosis or did not change into frogs at all.

The Pituitary.—Fichera[9] observed a constant hypertrophy of the pituitary body (hypophysis) in capons, oxen, buffaloes, and rabbits, castrated in early life—that is to say, an increase in weight by that organ as compared with the pituitary glands of other animals of the same kind, weight, and age. The increase in weight was associated with a rich blood supply, and an increase in the number of eosinophyl cells. These observations are confirmed for young dogs by Cimorini,[10] who states that the changes in the pituitary were similar to those occurring after removal of the thyroids. Tandler and Gross[1] have described pituitary hypertrophy in castrated men. The condition was found in the Skopzen sect of eunuchs and also in women after ovariotomy. Hammond[2] has shown that pituitary hypertrophy occurs in sheep after ovariotomy. It affects the glandular part or anterior lobe only. Blair Bell[3] finds evidence of increased secretory activity on the part of the anterior lobe of the pituitary after ovariotomy, but in his experience the changes are slight and not quite constant. They are not nearly so great as during pregnancy or after the removal of the thyroids or suprarenals. According to Livingston[4] whereas ovariotomy may cause hypertrophy of the pituitary in rabbits, the effect of castration on that organ is negligible. According to Pepere,[5] there is probably no specific hypertrophy of the hypophysis in relation to the extirpation of any particular ductless gland in the organism, but the reaction of the cellular elements, though varying in response to different conditions, shows also many characters referable to a common cause.

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[1] Calzolari, "Recherches experimentales sur un Rapport probable entre la Fonction du Thymus et celle des Testicules," *Arch. Ital. de Biol.*, vol. xxx., 1898.

[2] Ranzi and Tandler, "Ueber Thymus Extirpation," *Wien. klin. Woch.*, vol. xxii., 1909.

[3] Gellin, "Die Thymus nach Extirpation, etc.," *Zeitsch. f. exp. Path. und Pharm.*, vol. viii., 1910.

[4] Klose and Vogt, "Klinik und Biologie der Thymusdrüse," *Beitr. zur klin. Chir.*, vol. lxix., 1910.

[5] Manassini, "Sur les Modifications que la Castration peut determiner dans les Organes glandulaires, etc.," *Arch. Ital. de Biol.*, vol. liii., 1910.

[6] Squadrini, "Il comportamento del timo nelle varie della Vita postpetali nei Bovini," *Pathologica*, vol. ii., 1910.

[7] Valtorti, "Timo et Ovari," *Ann. di Ostet.*, vol. xxix., 1907, and vol. xxxi., 1909.

[8] Gudernatsch, "Feeding Experiments on Tadpoles," *Arch. f. Entwick.-Mech.*, vol. xxxv., 1913, and *Amer. Jour. of Anat.*, vol. xv., 1914.

[9] Fichera, "Sulla ipertrofia della glandula Pituitaria consecutiva castrazione," *Policlinico*, vol. xii., 1905.

[10] Cimorini, "Sur l'Hypertrophie de l'Hypophyse cérébrale chez les Animaux thyréoïdectomisés," *Arch. Ital. de Biol.*, vol. xlviii., 1907.

Compte[6] showed that the anterior lobe undergoes hypertrophy during pregnancy, the whole organ being increased in weight at the end of the period. Erdheim and Stumme[7] confirmed and extended the observations. The changes are due mainly to the accumulation of the "pregnancy cells" which are derived from the chromophobe or chief cells. Blair Bell[8] regards these pregnancy cells as being correlated with an immediate demand for increased secretion. The secretory products appear to pass over, at anyrate to some extent, to the posterior lobe. Pituitary hypertrophy during pregnancy may be so great as to cause pressure on the optic chiasma and transient pathological symptoms which disappear later when the gland returns to the normal condition.

It has been shown, as will be described more fully in the chapter on lactation (p. 621), that extract of posterior lobe when injected into the circulation has an immediate galactogogue effect, milk being copiously secreted if the mammary glands are in a state of lactation. The same effect occurs as a result of injecting extract of corpus luteum. Experiments have shown that ovariotomy results in persistent lactation if the operation be performed during the suckling period (see p. 614). It seems possible, therefore, that after ovariotomy the function of the corpus luteum in respect of mammary secretion is taken over by the pituitary vicariously, and that this organ when hypertrophied (unlike the corpus luteum) continues to exert an influence upon the mammary activity which may be continued indefinitely.[1]

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[1] Tandler and Gross, "Einfluss der Kastration, etc.," *Wien. klin. Woch.*, vol. xx., 1907. Tandler, "Untersuchungen an Skopzen," *Wien. klin. Woch.*, vol. xxi., 1908.

[2] Hammond, "The Effect of Pituitary Extract on the Secretion of Milk," *Quar. Jour. Exp. Phys.*, vol. vi., 1913.

[3] Blair Bell, *loc. cit.*

[4] Livingston, "Effect of Castration on Weight of Pituitary in Rabbits," *Proc. Soc. Exp. Biol. and Med.*, vol. xi., 1914; and *Amer. Jour. Physiol.*, vol. xl., 1916.

[5] Pepere, "Sur les Modifications de Structure du Tissu Parathyroidien normal et accessoire (thymique) en rapport avec sa Fonction vicariante," *Arch. de Méd. Expér.*, vol. xx., 1908.

[6] Compte, *Contribution a l'Étude de Hypophyse, etc.*, Lausanne, 1898; and *Beitr. zur Path. Anat., etc.*, vol. xxiii., 1898.

[7] Erdheim and Stumme, "Ueber die Schwangenschaftveraenderung der Hypophyse," *Beitr. zur Path. Anat., etc.*, vol. xlvi., 1909.

[8] Blair Bell, *loc. cit.*

Crowe, Cushing, and Homans,[2] as a result of a series of experiments on hypophysectomy on dogs, have shown that partial removal of the anterior lobe was followed by hypoplasia of the generative organs or persistent infantilism if the operation was done before puberty. There was a tendency to adiposity such as often occurs after castration. Aschner[3] obtained similar results. Puppies operated upon remained completely impotent and spermatogenesis did not occur in the male, neither did ovulation nor œstrus in the female. Hypophysectomy during pregnancy prevented the further development of the fœtus. Blair Bell found atrophic changes in the ovaries and uterus after partial removal of the anterior lobe. Clamping the infundibular stalk caused even more intense atrophy.

Goetsch[4] has obtained converse results by the administration of pituitary extract (in particular of anterior lobe which he states to be the responsible factor). Young rats fed with extract showed increased development and activity of the reproductive organs as compared with the controls. The Graafian follicles ripened more quickly. The uterine mucosa developed active glands, and there was increased vascularity over the whole generative tract. Extract of posterior lobe had no effect.

Clinical observations point clearly to similar conclusions. Hyperpituitarism due to overactivity of the anterior lobe and manifested histologically by a great increase in the eosinophile or acidophile cells, if commencing before puberty results in giantism, and if postadolescent causes acromegaly or an overgrowth of the bones of the face. In the former case it is associated with premature sexuality and in the latter with excessive sexual desire. However, after a period of hyperactivity on the part of the pituitary, retrogressive changes set in with that organ, and these are accompanied or followed by impotence and atrophy in the reproductive organs.[1]

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[1] This hypothesis assumes a functional connection between the anterior and posterior lobes (see p. 382).

[2] Crowe, Cushing, and Homans, "Experimental Hypophysectomy," *Johns Hopkins Hosp. Bull.*, vol. xxi., 1910. Cushing, *The Pituitary Body and its Disorders*, New York, 1912.

[3] Aschner, "Ueber die Funktion der Hypophyse," *Pflüger's Arch.*, vol. cxlvi., 1912.

[4] Goetsch, "The Relation of the Pituitary Gland to the Female Generative Organs," *Surg., Gyn. and Obstet.*, vol. xxv., 1917.

The Pineal.—Precocious sexual development associated with early secondary sexual changes (growth of pubic hair, enlargement of larynx, etc.) and general body growth is said to be correlated with hyperactivity in the pineal gland, but the evidence is very incomplete. Moreover, according to M'Cord[2] the administration of pineal extract to young Mammals is reported to hasten growth and sexual maturity. When given to unicellular animals (*Paramœcium*) the rate of reproduction was markedly increased, and when fed to tadpoles, growth and metamorphosis were hastened. On the other hand, according to Biach and Hulles,[3] castration in kittens caused atrophy of the pineal, and according to Foà[4] removal of the pineal in the young cockerel caused sexual precocity and an earlier development of the secondary male characters.

The Thyroid.—It is well known that there is a correlation between the sexual organs and the thyroids. These glands undergo enlargement during menstruation and pregnancy in women, and Freund[5] has shown that similar changes occur during the heat periods of many of the lower Mammals. He has pointed out further, that swelling of the thyroid, at the time of puberty, often leads to goitre, and that this disease commonly begins at a period of menstruation. M'Carrison[6] states that the sexual act and marriage in both sexes increases the gland's activity and that the consequent swelling is well known to primitive races. Arbuthnot Lane[7] also says that swelling is associated with intercourse as well as with pregnancy, and that it alters with the intensity of the sexual appetite. Such facts are cited by Gaskell[8] as evidence of a special connection between the thyroid and the sexual organs—the former being held to represent the uterus of the scorpion. Alquier and Thauveny[9] state that after the partial or complete removal of the thyroids and parathyroids menstruation and conception are very infrequent, but this result may be due to the general metabolic disturbance arising from the absence of the glands. Blair Bell found that after thyroidectomy in the cat the uterus underwent atrophy similar to that observed after the removal of the ovaries. According to the same author there is in Rodents a considerable increase in the functional activity of the thyroid in regard to colloid production after ovariotomy. It is stated also that the colloid is basophile instead of eosinophile and this change is regarded as representing a storage secretion formed to meet the altered conditions of metabolism. According to Leo Loeb[1] almost complete thyroidectomy during pregnancy does not always necessarily lead to abortion, but no hypertrophy was found in the thyroids of the fœtuses.

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[1] See also Woods Hutchinson, "The Pituitary Gland as a Factor in Acromegaly and Giantism," *New York Med. Jour.*, 1900.

[2] M'Cord, "The Pineal Gland," *Surg., Gyn. and Obstet.*, vol. xxv., 1917.

[3] Biach and Hulles, "Ueber die Beziehungen der Zurbeldrüse zum Genitale," *Wien. klin. Woch.*, vol. xxv., 1912.

[4] Foà, "Hypertrophie des Testicules et de la Crête apres l'Extirpation de la Glande Pineale chez le Coq," *Arch. Ital. de Biol.*, vol. lvii., 1912.

[5] Freund, "Die Beziehungen der Schilddrüse zu den weiblichen Geschlechtsorganen," *Deutsche Zeitsch. f. Chir.*, vol. xviii., 1883.

[6] M'Carrison, *The Thyroid Gland*, London, 1917.

[7] Lane, *Guy's Hospital Gazette*, vol. xxxii., 1918.

[8] Gaskell, *The Origin of Vertebrates*, London, 1908.

[9] Alquier and Thauveny, "État de l'Ovaire de Chiennes ayant l'Extirpation partielle ou totale de l'Appareil Thyro-Parathyroïdien," *C. R. de la Soc. de Biol.*, vol. lxvi., 1910.

The Parathyroid.—According to Pool,[2] the efficiency of the parathyroid is affected by the œstrous cycle, for tetany, which is the clinical manifestation of parathyroid insufficiency, is especially prone to occur during menstruation, pregnancy, or the puerperium, when the parathyroids fail to adjust themselves to an increased metabolism. Blair Bell states that castration may prevent tetany in cats from which the thyroids and most of the parathyroids have been removed, and this result is ascribed to a retention of calcium. In maternal tetany calcium in large doses has a beneficial result.

The Suprarenal.—There is some evidence of a correlation existing between the sexual organs and the suprarenals. Thus Gottschau[3] states that in rabbits changes occur in these organs during pregnancy, the outer zone of the cortex becoming twice its normal thickness, whereas the medulla is said to become thinner. Similarly, Stilling[4] states that in frogs during the pairing time the medulla disappears, while characteristic cells known as "summer cells" become developed. Bulloch and Sequeira[5] state that in cases of children with carcinomata of the suprarenals, this is associated with premature development of the genital organs and the accessory generative glands. According to Glynn,[6] adrenal hypernephromata are generally associated with sexual precocity and overgrowth of hair in children.

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[1] Loeb, "Studies on Compensatory Hypertrophy of the Thyroid Gland," I., *Jour. Med. Research*, vol. xl., 1919.

[2] Pool, "The Relation of the Parathyroid System to the Female Genital Apparatus," *Surg., Gyn. and Obstet.*, vol. xxv., 1917.

[3] Gottschau, "Ueber Nebennieren der Saügethiere, etc.," *Sitz.-Ber. d. phys. med. Gesell. zu Würzburg*, vols. xvii.-xviii., 1882.

[4] Stilling, "Zur Anatomie der Nebennieren," *Arch. f. Mikr. Anat.*, vol. lii., 1898.

[5] Bulloch and Sequeira, "On the Relation of the Suprarenal Capsules to the Sexual Organs," *Trans. Path. Soc.*, vol. lvi., 1905.

[6] Glynn, "The Adrenal Cortex, its Rests and Tumours; its Relation to other Ductless Glands, and especially to Sex," *Quar. Jour. of Med.*, vol. v., 1912.

R. G. and A. D. Hoskyns[1] state that feeding rats on desiccated suprarenal gland led to the hypertrophy of the gonads.

The evidence as to the effect of castration on the suprarenals is conflicting.[2]

It is thus seen that there is evidence of very definite functional correlation between the gonads and the other organs of internal secretion. In some cases this appears to be of the nature of a potential compensatory arrangement; in others it would seem rather that the glands act antagonistically. In the present state of our knowledge it is hardly possible to formulate any general scheme which embraces all the known facts, and such attempts as have been made in this direction have in our judgment been premature.[3]

General Conclusions regarding the Internal Secretions of the Ovary and the Testis

It will be convenient at this point to summarise the conclusions which have been tentatively arrived at concerning the nature and purpose of the internal secretions of the ovary and the testis.

The mammalian ovary, in addition to its oögenetic function, is an organ elaborating a chemical substance or substances which react on the general metabolism and control the nutrition of the uterus and, at any rate to some extent, of the mammary glands. The secretion is probably produced by the cells of the follicular epithelium, or by the interstitial cells of the stroma, or, perhaps, by both combined.[4] It is formed in greater or less quantity at all times, but is produced in increased abundance at certain recurrent periods, when it brings about those conditions of growth and hyperæmia which characterise the prœstrous processes. It is at these periods also, in typical cases, that the follicles become mature. After ovulation, which occurs during œstrus, the secretory cells of the ovary show still greater activity, and become converted by a process of simple hypertrophy into the luteal cells of the corpus luteum. If the ovum is fertilised, these cells continue to increase in size until nearly mid-pregnancy (or, in some animals, a somewhat earlier period), but later they undergo degeneration. If pregnancy does not supervene, the luteal cells in polyœstrous animals under normal conditions begin to degenerate at a much earlier period and without attaining their full development. In monœstrous animals the corpus luteum persists for an approximately equal time under conditions of pregnancy or pseudo-pregnancy. The pronounced hypertrophy of the follicular epithelial and interstitial cells, which takes place at the beginning of pregnancy, is directly correlated with a nearly simultaneous hypertrophy on the part of the uterus and of the mammary glands. The corpus luteum, therefore, is to be regarded as an essential factor in maintaining the raised nutrition of the uterus during a part at least of the period of gestation; it is also responsible for stimulating the growth of the mammary tissue preparatory to the secretion of milk. When the later part of gestation is reached, the ovarian secretion has probably been already formed in sufficient quantity to prevent the uterus from lapsing into the normal condition until the end of pregnancy. It is to be noted, however, that fibrous degeneration has been described in the maternal placenta in the later stages of its existence.

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[1] Hoskyns (R. G.) and Hoskyns (A. D.), "The Effects of Suprarenal Feeding," *Arch. Int. Med.*, vol. xvii., 1916.

[2] See Swale Vincent, "The Experimental and Clinical Evidence as to the Influence Exerted by the Adrenal Bodies upon the Genital System," *Surg., Gyn. and Obstet.*, vol. xxv., 1917. See also de Mira, "Sur l'état des Capsules Surrénales chez les Animaux Ovariectomisés," *Bull. Soc. Portugaise des Sci. Nat.*, vol. vi., 1912.

[3] See Swale Vincent, *Internal Secretion and the Ductless Glands*, London, 1922. Noel Paton, *The Nervous and Chemical Regulation of Metabolism*, London, 1913. Biedl, *loc. cit.*, and Blair Bell, *loc. cit.*

[4] Limon (*loc. cit.*) suggested, as a result of his experiments in grafting, that the ovarian secretion is elaborated by the interstitial cells. It should here be remembered that the follicular epithelial and interstitial cells are almost certainly identical by origin, and so probably similar potentially (p. 114), and that both of these cellular elements have been described as taking part in the formation of the corpus luteum (p. 142); and also, that those interstitial cells which do not form part of the corpus luteum have been stated to undergo an independent hypertrophy during pregnancy (p. 156); *cf.* Steinach and Lipschütz on the "puberty gland" (see above, p. 346). Bucura (*loc. cit.*) regards the follicular epithelium, the interstitial cells, and the corpus luteum as alike in producing sexual hormones.

Thus the ovaries pass through a series of cyclical changes which are directly correlated with those undergone by the uterus and mammary glands. The ovarian changes are always the cause; the uterine and mammary changes are the effects. Moreover, the uterus atrophies after ovariotomy. Whether or not the corpus luteum (which may persist for a time even after parturition) is a factor in actual milk secretion is an open question, but the influence of luteal extract on this process is suggestive of a connection.

It seems probable that this close co-ordination between the ovarian and uterine functions arose very gradually in evolutionary history, and it may be that in the aplacental Mammals we have in existence at the present day an intermediate stage in the development of this relation. Starling[1] has suggested that the internal secretions, or hormones generally, arose at first as products of ordinary metabolic activity in certain particular tissues, and that the evolution of the various cases of chemical correlation between different organs in the body came into existence, not by the production on the part of certain tissues of special substances acting as chemical messengers, but by the acquisition of a specific sensibility on the part of other functionally related tissues. It is no doubt possible that the chemical co-ordination of the ovarian and uterine activities arose partly in this way; but, on the other hand, the definite character of certain of the cyclical changes which take place in the ovary, and particularly those which relate to the formation of the corpus luteum, points to the conclusion that the secretory function of the ovary has been perfected, or at any rate has undergone great development in the phylogenetic history of the Mammalia, though it no doubt existed previously in a minor degree.

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[1] Starling, "The Chemical Co-ordination of the Activities of the Body," *Science Progress*, vol. i., (April) 1907.

As to whether the ovary elaborates more than one specific substance acting as a chemical excitant, there is some evidence,[1] and the composition of the corpus luteum (which is different from that of the rest of the ovary) indicates that the formation of this structure is accompanied by a change in the nature of the ovarian secretion. Lastly, it is possible that the influence of the ovary upon the metabolism is due partly to this organ being excretory as well as secretory in function, but there is no evidence that this is actually the case.

The fact that the testis is an organ of internal secretion seems also to be definitely proved. This secretion is probably formed throughout the entire reproductive period of an animal's life; but, in those animals which experience a periodic rut, it is no doubt at this season that the testicular hormone is produced in greatest abundance. The development of the prostate and the secondary sexual characters, not to mention the growth of the testes themselves, is convincing evidence that this is so. The hormone is apparently produced by the interstitial cells (at least in Mammals).

THE INFLUENCE OF THE REPRODUCTIVE ORGANS AND THE EFFECTS OF CASTRATION UPON THE GENERAL METABOLISM

In view of the facts referred to above it is almost self-evident that castration must exercise some influence upon the general metabolism of the body, since it produces such marked effects upon the primary and secondary sexual characters. Moreover, it is commonly believed that the removal of the reproductive glands causes a tendency towards obesity both in man and animals, but it is not quite clear whether this occurs as a direct or an indirect consequence of castration. However this may be it seems certain that sows which have been spayed fatten faster and thrive better than those left unoperated upon, but this result may be due to their feeding more regularly and without disturbance from recurrent œstrous periods.[1] The deposition of fat which is so often seen after the menopause is to be regarded as further evidence of a connection between the functional ovaries and the general metabolism.

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[1] See below, p. 621, Chapter XIII.

The existence of such a functional correlation is shown more clearly by the effects of ovariotomy upon the bone disease known as osteomalacia.[2] The ovaries undoubtedly exert a marked influence over the phosphorus metabolism, and the improvement which sets in after the removal of these organs in cases of osteomalacia is apparently brought about by a retention of the earthy phosphates whereby the skeletal tissues acquire their normal rigidity. Unfortunately, the experimental work which has so far been done upon the phosphorus and calcium metabolism in normal and castrated animals is too contradictory to admit of the deduction of any conclusions that are calculated to throw much light upon the phenomena of osteomalacia.[3] Blair Bell,[4] however, records a reduction of fifty per cent. in the calcium excretion of cats after ovariotomy, and with this he correlates the fact that in young animals there is generally an increase in the length of the long bones after ovariotomy, as well as the just mentioned case of osteomalacia being cured by the same operation.

The protein metabolism of castrated animals has been investigated by Lüthje,[5] who records no changes as a consequence of the removal of the generative glands. Certain other investigators, as a result of shorter series of experiments, have obtained trifling effects, sometimes showing a slight increase in the nitrogenous output and sometimes a diminution.[6]

Experiments upon the respiratory exchange have been almost equally inconclusive, and have so far failed to show any constant alteration as a consequence of castration. This question is discussed at some length by von Noorden,[7] who calls attention to the necessity for distinguishing whether the total daily metabolism, which in some cases has been shown to become diminished after castration, does so in consequence of a variation in temperament (or greater tendency towards physical repose), or whether the oxidation of the resting cell (*i.e.* the fundamental metabolism) is reduced. He is disposed to believe that the marked diminution in the respiratory exchange which has been observed in some animals after castration is probably due to a greater indolence, and is, therefore, an indirect result. Moreover, he points out that, in the case of Lüthje's castrated dogs, which did not exhibit any change from their normal habits and movements, there was no diminution in the gaseous exchange as compared with control animals.

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[1] Mackenzie and Marshall, "Physiology and Bacon Curing," *Jour. Roy. Agric. Soc.*, vol. lxxvi., 1915. See also "On Ovariotomy in Sows," *Jour. Agric. Soc.*, vols. iv., v., vi., vii., 1911-16.

[2] In one case of osteomalacia Krönig removed the ovaries and transplanted them on to the peritoneum. The result was immediately beneficial ; but with the return of menstruation, which followed after about two months, the symptoms of the disease are said to have reasserted themselves (Stuttgart Medical Congress, *Zeitsch. f. Gynäk.*, 1906). See also Fraenkel, "Ovarialantikorper und Osteomalacia," *Münch. med. Wochenschr.*, No. 25, 1908.

[3] Von Noorden, *Metabolism and Practical Medicine*, English Edition, edited by Walker Hall, vol. i., London, 1907 (see above, p. 298). According to Wallart, "Ueber das Verhalten der interstiellen Eierstocksdrüse bei Osteomalacia," *Zeitsch. f. Geb. und Gynäk.*, vol. lxi., 1908, osteomalacia is correlated with an increase of the interstitial cells in the ovary.

[4] Blair Bell, *loc. cit.*

[5] Lüthje, "Ueber die Kastration und ihre Folgen," *Experim. Archiv*, vol. xlviii., 1902, and vol. l., 1903.

[6] Von Noorden, *loc. cit.*

[7] *Ibid.*

Loewy and Richter,[1] however, have arrived at different conclusions, finding pronounced reduction in the respiratory metabolism of castrated dogs of both sexes. Furthermore, these investigators found that after feeding the female animals upon ovarian substances there was a great increase in the metabolism, a castrated bitch showing an increase of from thirty to fifty per cent. above the normal values observed before the operation. Testicular substance had no influence upon any of the castrated animals, while normal animals did not react at all either to ovarian or to testicular extracts. Loewy and Richter suggest that the ovaries produce a specific substance which promotes oxidation in the body.

Zuntz[2] has investigated the gaseous metabolism in four castrated women, and found that it lay within the limits of the normal. It is to be noted that neither of these women showed any tendency to corpulence. These observations support the view that when castrated animals show a reduction in the respiratory exchange, this is an indirect effect resulting from greater indolence of disposition. On this view, also, the tendency towards a deposition of fat on the part of many castrated animals is to be attributed to the same cause.

Dr. Cramer,[3] working in conjunction with the author, has lately investigated the respiratory metabolism of a number of rats whose ovaries had been removed some time previously, and in these animals it was found that the gaseous exchange lay within the limits of the normal, thus confirming Zuntz's experience with castrated women. It is possible, however, that the results of castration were obscured by other factors. In this investigation the apparatus employed by Haldane and Pembrey was used in preference to that of Zuntz. We did not observe any marked tendency to deposition of fat in the castrated rats.

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[1] Loewy and Richter, "Sexual-Funktion und Stoffwechsel," *Arch. f. Physiol.*, Supplement, 1899.

[2] Zuntz, "Gaswechsel bei Kastrierten Frauen," *Verhandl. d. Gynäk. Gesell.*, Berlin, 1904. See also *Deutsch. Zeitsch. f. Chir.*, vol. 65, 1908.

[3] Cramer and Marshall. MS. unpublished.

Furthermore, it is to be noted that, according to Magnus-Levy and Falk,[1] the period of puberty in boys and girls is not associated with any increase in the gaseous metabolism.

Murlin and Bailey,[2] however, obtained results upholding those of Loewy and Richter so far as the reduction in metabolism after castration is concerned. Ovariotomy in dogs was followed by an increase in weight and an average lowering of the metabolism of about twelve per cent. The animals were fed on a constant diet of meat, cracker meal, and lard. The metabolism was estimated by an indirect method, using Murlin's constant temperature respiration incubator and weighing the oxygen entering and the carbon dioxide and water leaving the box. A sample of the residual air of the cage was also weighed at the end of each period. The urine was analysed for nitrogen and the amount included in the result.

Moreover, Kojima[3] states that twenty-two and forty-eight days after castration in rats the animals showed a marked diminution in CO_2 output. The appetite and weight increased.

Certain further experiments upon the effects of administering ovarian extract may also be referred to here. Neumann and Vas[4] record losses of nitrogen, phosphorus pentoxide, and calcium monoxide after injecting glycerine extract of ovary subcutaneously. Loewy[5] and Neumann found no change in the nitrogen metabolism in castrated animals after administering ovarian extracts, but Neumann observed a loss of phosphorus pentoxide and calcium monoxide in the fæces. Sack[6] found that injection of corpus luteum extract produced a nitrogen retention in the female, but not in the male, thereby confirming the view that the corpus luteum must act on the uterus, or mammary gland, or both. Certain other less satisfactory experiments, dealing with more or less contradictory observations, are briefly referred to by von Noorden.

Mackenzie Wallis and Everard Williams[7] have recently carried out what appears to be a very important investigation upon the corpus

[1] Magnus-Levy and Falk, "Lungengaswechsel des Menschen," *Arch. f. Physiol.*, Supplement, 1899.

[2] Murlin and Bailey, "Relation of the Sex Glands to Metabolism," *Surg., Gyn. and Obstet.*, vol. xxv., 1917.

[3] Kojima, "Studies on the Endocrine Glands," V., *Quar. Jour. Exp. Physiol.*, vol. xi., 1917.

[4] Neumann and Vas, "Einfluss der Ovariumpräparate auf den Stoffwechsel," *Monatsschr. f. Geburtsh. u. Gynäk.*, vol. xv., 1902.

[5] Loewy, "Ueber den Einfluss des Oophorins," *Berl. klin. Wochenschr.*, 1899.

[6] Sack, "Ueber den Einfluss von Corpus Luteum und Hypophyse auf den Stoffwechsel," *Arch. für. Exp. Path. und Pharm.*, vol. lxx., 1912.

[7] Wallis and Williams, "An Experimental Investigation upon the Corpus Luteum in Relation to the Toxæmias of Pregnancy," *Lancet*, vol. ccii., (22nd April) 1922.

luteum in relation to the toxæmias of pregnancy. By alcoholic extraction from the fresh gland obtained from the ovaries of sows and in some cases from women, they have prepared and isolated a chemical substance which, when injected into animals, produces necrosis and other changes similar to the toxæmias. Extracts of placenta and of hydatiform mole, on the other hand, were found to be non-toxic. The authors believe that the toxæmias which so often occur in pregnancy are due to hyperactivity of the corpus luteum, and they suggest further that it is the secretion from this organ which reacts on the thyroid and stimulates it to growth and hyperactivity. The excess of cholesterol during pregnancy is regarded also as an attempt to neutralise the toxic effect of the corpus luteum. The active principle was protein free, but it appeared to be associated with a lipoid. Cholesterol, choline, histamine, and tyramine were absent. "The highly refractile solution was found to undergo destruction with the serum of a pregnant woman." The test was likewise positive during the early stages of menstruation, but otherwise with non-pregnant women it was negative, as it was also with males. The changes were observed by means of the refractometer.

The influence of castration upon the blood has formed the subject of a research by Breuer and Seiler,[1] who employed bitches whose ovaries were removed shortly after puberty. They record marked diminution in the hæmoglobin and the red cells.[2]

In concluding this brief summary of the recorded results of castration, and the influence of the generative organs upon the metabolism, the necessity for further investigation must be emphasised, since it is hardly possible that the totality of the effects produced is of as slight a nature as the accepted evidence at present seems to indicate.[3]

[1] Breuer and Seiler, "Einfluss der Kastration auf den Blutbefund weiblicher Tiere," *Experim. Archiv*, vol. l., 1903.

[2] It has also been stated that castration may improve the quality of the milk (Oceanu and Babes, "Les Effets Physiologiques de l'Ovariotomie chez la Chèvre," *C. R. de l'Acad. des Sciences*, vol. cxl., 1905). For some account of the effects of disease in the ovaries and other reproductive organs upon the rest of the body, see Wilson, "The Reciprocal Relations between the Affections of the Uterus and its Appendages upon the Rest of the Body" (*Lancet*, Part II., November 1906). Further references are given in this paper.

[3] For a full bibliography see Barker, *Endocrinology and Metabolism*, New York and London, 1922. For further experimental work on sexual characters see Zawadowsky, *Das Geschlecht und die Entwickelung das geschlechtmerkmale*, Moscow, 1922. (The work is written in Russian.)

It has been found that ovariotomy performed in young Herdwick lambs does not result in horn growth, though in one animal small scurs were formed; such scurs are said, however, sometimes to occur normally in Herdwick ewes (Marshall, *Proc. Roy. Soc.*, B., vol. lxxxv., 1912; *cf.* p. 323 above).

CHAPTER X[1]

FŒTAL NUTRITION: THE PLACENTA

"Birth . . . is commonly considered as the point at which we begin to live. More truly it is the point at which we leave off knowing how to live. . . . Not but what before birth there have been unsettled convictions (more's the pity) with not a few."—SAMUEL BUTLER.

PART I

THE PLACENTA AS AN ORGAN OF NUTRITION

I. HISTORICAL SURVEY

THE mammalian ovum, in all except the Monotremata, is small and does not contain a sufficient supply of nutriment for the developing embryo. It is retained for a longer or shorter period in the uterus, where, by special modifications of the uterine mucosa and a part of the ovum, the placenta is formed, and a transmission of nutriment from the mother to the embryo is made possible. The changes in the maternal and embryonic tissues vary greatly in the several orders, and even in groups of the same order, but in all they are sufficiently complicated to render their explanation a matter of great difficulty. It is doubtful if any anatomical structure has given rise to keener or more prolonged controversies than the placenta.

We owe to Harvey[2] the conception of the placenta as an organ elaborating from the maternal blood the aliment necessary for the growth and development of the fœtus. He was the first to reject the "subtleties and fanciful conjectures" on embryonic development, and to advocate and practise direct and diligent observation. But for a century after his death the placenta received little notice. With the introduction of the microscope the attention of biologists was directed towards the origin and development of the embryo, and it was then that the ovarian vesicles and spermatozoa were first observed.

In the second half of the eighteenth century were published the researches of John and William Hunter on the human placenta, important not only in themselves, but as destined to set agoing the vast amount of work done in the first half of the nineteenth century. John Hunter[1] stated that the maternal blood circulated through the placenta, and this view, which, according to Waldeyer,[2] had formerly been held by Vater and Noortwyk, though the latter at least believed in the communication of the maternal and fœtal circulations, was supported by the subsequent dissection of injected placentæ by John Hunter and his brother. The statement of the former that "the blood of the placenta is detached from the common circulation of the mother, moves through the placenta, and is then returned back into the circulation of the mother," gave rise later to a considerable amount of discussion. They showed that the decidua was uterine and not fœtal, and the decidua reflexa was first figured in one of William Hunter's plates.[3]

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[1] By James Lochhead.

[2] Harvey, *The Generation of Animals*, London, 1651.

It is remarkable that John Hunter did not recognise the placenta as the organ of fœtal respiration. A century before, Mayow[4] had declared that the placenta functioned as a fœtal lung, the umbilical vessels taking up the nitro-aerial gas (oxygen) and carrying it to the fœtus. This view was adopted by Ray,[5] who compared the villi lying in the maternal sinuses to the gills of a fish in the water. The first to take up Priestley's discovery of oxygen, and state definitely that it was *oxygen* that went constantly from mother to fœtus, and whose absence caused fœtal asphyxia, was Girtanner in 1794. But all doubt was not removed till, in 1874, the spectroscopic bands of oxyhæmoglobin were demonstrated in the umbilical vein of a guinea-pig by Albert Schmidt, a pupil of Preyer.[6]

The work of the brothers Hunter was carried on by Weber, Goodsir, Coste, Eschricht, Reid, and others. Of the many investigations, none had such an important influence as the researches of Goodsir.[7] He first studied the placental *cells* with regard to their function. His predecessors had spoken in the vaguest terms of the passage of nutriment from mother to fœtus, but Goodsir had definite ideas. He described the villi as having two covering layers of cells, an external system belonging to the decidua, and an internal belonging to the chorion. As to their function, he says: "The external cells separate from the blood of the mother the matter destined for the blood of the fœtus they are secreting; the internal cells absorb the matter secreted by the agency of the external cells." Thus we have the active part of placental metabolism referred for the first time to the cells of the villi.

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[1] Hunter (J.), *Observations on Certain Parts of the Animal Economy*, Edit. by Palmer, vol. iv.

[2] Waldeyer, "Bemerkungen über den Bau der Menschen- und Affenplacenta," *Arch. f. mikr. Anat.*, vol. xxxv., 1890.

[3] Hunter (W.), *Anatomy of the Human Gravid Uterus*, Birmingham, 1777.

[4] Mayow, *Tractus Tertius de Respiratione Fœtus in Utero*, 1674.

[5] Ray, *The Wisdom of God in the Creation*, 12th Edition, 1754.

[6] See Preyer's *Specielle Physiologie des Embryo*, 1883.

[7] Goodsir, *Anatomical and Pathological Observations*, Edinburgh, 1845.

The importance of the intervillous spaces for fœtal nutrition was first emphasised by Weber,[1] and they were the subject of close attention. The Hunterian doctrine that in the human placenta they contained blood was not yet established, and their mode of development gave rise to a long-continued controversy. John Hunter considered them outwith the maternal vascular system, and his view was supported by Owen,[2] Kölliker,[3] and Farre.[4] Weber and Reid[5] held that the spaces were bounded by a thin maternal membrane, and Goodsir described two layers of maternal tissue between the blood in the sinuses and the vessels of the villi.

The investigation of the intervillous spaces and the epithelial investment of the villi was carried on by Turner, Ercolani, Langhans, and many others. Turner[6] and Waldeyer looked on the intervillous spaces as dilated maternal capillaries; but while Turner held that the villi, at least in part, penetrated their endothelium, Waldeyer supposed that they pushed the endothelium before them, and so got a covering of this maternal layer. Langhans[7] regarded the spaces as formed by that part of the lumen of the uterus which lay between the surface of the mucosa and the chorion, and thought that the villi by eroding vessels came to be bathed in extravasations of maternal blood. Klebs[8] considered them to be lymph-spaces, and therefore extra-vascular; and Jassinsky[9] described them as being formed by the penetration of the villi into the maternal glands, whose epithelium came to clothe the villi externally. Now it has been proved from the examination of early ova that the intervillous spaces are entirely fœtal and are formed in the epiblast.

The investigations of Langhans proved to be the turning-point in the controversy regarding the investment of the villi. He showed that it consisted in the earlier stages of pregnancy of a double covering, a deep layer of cells (Langhans' layer), and superficially a mass of "canalised fibrin." The presence of fibrin had been noted by Weber and several of his successors; Winkler[1] proved it to be a constant phenomenon, and gave it the name "Schlussplatte"; but it was Langhans who first described its relations, and suggested its probable origin from the fœtal epiblast. The cellular layer, according to Langhans, was mesoblastic. Kastschenko[2] first described both layers as epiblastic, and showed that the outer layer was a *syncytium* or mass of nucleated protoplasm without cell-boundaries. Such investigations led to the feeling that the structure of the placenta could only be understood by tracing its development from very early periods of gestation. Hence the search for and examination of young human ova were stimulated, and the study of the uterine condition in age-series of pregnant animals was begun. Up to this time the chief controversies had raged around the human placenta. Comparative placentation had engaged the attention of few morphologists, among whom Turner, the "grand-master of placental research" (Hubrecht[3]), was *facile princeps.* But within recent years investigations have been carried out on many orders of placental Mammals. Of these the most important are the researches of Duval and Hubrecht, which have established that the discoid placenta is essentially "a maternal hæmorrhage encysted by fœtal elements."

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[1] See Wagner's *Elements of Physiology*, translated by Willis, London, 1841.

[2] See note in *John Hunter's Collected Works*, Edit. by Palmer, vol. iv.

[3] Kölliker, *Entwicklungsgeschichte*, 1861, 1884, etc.

[4] See *Tod's Cyclopædia*, Article "Uterus," 1858.

[5] Reid, "On the Anatomical Relations of the Blood-Vessels of the Mother to those of the Fœtus in the Human Species," *Edinburgh Medical and Surgical Journal*, vol. lv., 1841.

[6] Turner, "Some General Observations on the Placenta, etc.," *Jour. of Anat. and Phys.*, vol. xi., 1877.

[7] Langhans, "Untersuchungen über die menschliche Placenta," *Arch. f. Anat. u. Phys.*, Anat. Abth., 1877.

[8] Klebs (E.), "Zur vergleichende Anatomie der Placenta," *Arch. f. mikr. Anat.*, vol. xxxvii., 1891.

[9] Jassinsky, "Zur Lehre über die Struktur der Placenta," *Virchow's Arch.*, vol. xl., 1867.

II. Structure and Functions of the Epithelial Investment of the Villi

The cellular layer of the villi is a temporary structure, and disappears to a great extent comparatively early in pregnancy. It is generally looked on as the mother zone of the outer syncytial layer. Strahl[4] states, however, that in one of the new-world apes it is not present at a stage as early as that of Peters' human ovum, though a thick syncytial layer is present. Processes of it precede the mesoblastic outgrowths in the formation of the villi, and by a special proliferation of the cells at the tips of the villi, the "Zellsäulen" of Langhans, an attachment to the decidua is effected. While present, the cellular layer lies in the path by which the nutriment for the fœtus is carried to the villous capillaries, but it is not known whether it exerts any metabolic influence. Peters has suggested, without any very definite evidence, that it may have a coagulating action on maternal blood, necessitating the interposition of the syncytial layer.

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[1] Winkler (F. N.), "Zur Kenntnis der menschlichen Placenta," *Arch. f. Gynäk.*, vol. iv., 1872.

[2] Kastschenko, "Das menschliche Chorionepithel und dessen Rolle bei der Histogenese der Placenta," *Arch. f. Anat. u. Phys.*, Anat. Abth., 1885.

[3] Hubrecht, "The Placentation of *Erinaceus europæus*," *Quar. Jour. Micr. Science*, vol. xxx., 1889.

[4] Strahl, "Ueber Placentarsyncytien," *Anat. Anz.*, vol. xxix., Ergänzungsh., 1906.

The syncytium is more permanent. In the earliest human ovum yet examined it already constitutes a considerable mass, and a similar thickening over the whole or part of the circumference of the blastocyst occurs early in all the Deciduata. Where a decidua reflexa exists, the early proliferation appears to be related to the excavation of the cavity in which the ovum lies. In discoid placentæ the mass is vacuolated, and maternal blood is contained in the lacunæ. In the later stages of pregnancy it forms an attenuated membrane over the villi, and may wholly disappear at parts. The nuclei are numerous, and most of the authorities agree on the absence of mitoses, some holding that they divide directly, others that they have lost the power of division. The protoplasm has a foam-like structure, and in man it is condensed superficially to form a layer which bears the "Bürstenbesatz" or *striated border* (Fig. 98). This consists, as seen in fixed specimens, of a series of fine striæ running perpendicularly to the surface, and its structure and function have been much discussed since it was first described by Minot.[1] Some have denied its existence during life, and ascribed it wholly to the method of preparation. But Hofbauer[2] has shown that the fresher a specimen is when obtained, the easier it is to demonstrate the striæ by methods of staining, and, therefore, it is probably a vital structure. Kastschenko looked on the striæ as fine hairs which projected from the surface of the cells, and by their vibrations created a stream in the maternal blood of the intervillous spaces. In specimens stained

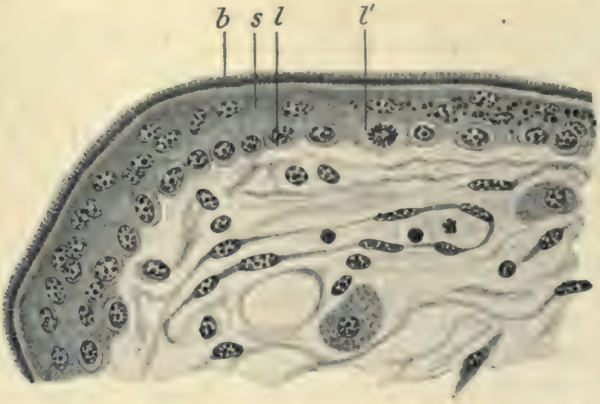

Fig. 98.—Part of an early human chorionic villus. (From Hofbauer's *Biologie der menschlichen Plazenta*, Braumüller.)

b, Bürstenbesatz with basal corpuscles ; s, syncytium ; l, Langhans' layer, one cell dividing mitotically (l′).

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[1] Minot, "Uterus and Embryo," *Jour. of Morphol.*, vol. xi., 1889.
[2] Hofbauer, *Biologie der menschlichen Plazenta*, Leipzig, 1905.

with iron-hæmatoxylin, knobs may be seen at the bases—basal corpuscles or blepharoblasts—and they may constitute the motor centre for the ciliary beats. But no movements have yet been observed, and von Lenhossék[1] calls them "stereozilien," or stationary cilia, suggesting that they may help to break down vessel-walls during the burrowing of the syncytium into the serotina. Sometimes they appear not to project free on the surface but to lie in the superficial stratum; then lighter and darker striæ alternate, and it is this appearance which has led to the name "striated edge." Bonnet[2] ingeniously remarks that it proves the fœtal origin of the syncytium, because, if it were uterine, the free edge would be formed by the bases of maternal cells, and they could not possess a "Bürstenbesatz." The same appearance has been noted in intestinal epithelium, but its significance is unknown. In the placenta Graf v. Spee[3] attributes the appearance to the teasing out of the surface of the protoplasm, and looks on it as evidence of a strong flow of fluid through the syncytium. It has also been suggested that the thin rods may be hollow and act as pores by which nutriment may enter the syncytium, or by which a secretion of the syncytium may pour out in order to prepare the constituents of the maternal blood for their transference to the fœtus.

It is still undecided whether the syncytium possesses amœboid motility. V. Lenhossék examined a human ovum several minutes after its removal from the uterus and observed, as has already been stated, no ciliary movements; but he considered it not improbable that the syncytium underwent changes of form. Hofbauer tried unsuccessfully to demonstrate such movements in a specimen examined immediately after its removal.

The core in young villi consists of a matrix, homogeneous or delicately fibrillated. In it are placed the blood-vessels and connective tissue corpuscles with long branching processes, which form a network in the matrix, and probably provide a series of lymph-channels. Kastschenko also described special cells, with large nuclei, which he took to be wandering cells. But Lenhossék proved that they existed before leucocytes or lymph-cells appeared, and must, therefore, be formed in the villi and derived from mesoblastic cells. Hofbauer has observed them also in the lumen of the fœtal vessels, and suggests a possible transformation to leucocytes.

Our ideas upon the function of syncytia are largely based on the investigations of His:[1] "They are not really specific tissue structures, but tissue conditions requiring definite phases of protoplasmic vitality. They occur along with a high degree of activity—with increased absorption and action on material—as well as with increased motility. Favourable conditions of nutrition form the fundamental condition for the existence of syncytia, and such conditions are certainly well offered in the uterus." At the present time the syncytium is regarded as of the highest importance in fœtal nutrition. Strahl[2] and Heinricius,[3] noting its gradual and progressive diminution as pregnancy advanced, supposed that it formed a part of the nutriment for the embryo, but this idea has not been adopted. The general theory is that it is essential in maintaining the interchange of material between mother and fœtus. The substances necessary for the building up of the fœtal body may be divided into two groups—diffusible and non-diffusible. The passage of the former can be explained by physical laws, but it is different with the non-diffusible or colloid substances. This is a difficulty which does not belong to the placenta alone, but to every organ of the body, and authorities are divided between two theories, the mechanical and the vital. The supporters of the mechanical theory hold that all the processes occurring in the placenta are possible by the laws of filtration and osmosis, and they have carried out numerous experiments to prove that substances in solution may pass across the placenta in both directions. Others, paying special attention to the nature of the barrier formed by the epithelial covering of the villi, deny that by such physical processes the non-diffusible substances with large molecules, *e.g.* hæmoglobin and other blood proteins, can be absorbed by the syncytium. They postulate a vital action on the part of the cells, by which the necessary material is selected by the syncytium, and altered to a form in which it may be transmitted to the fœtal circulation. It is not yet settled whether the activity of the syncytium is due to a phagocytic power or to an enzyme action.

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[1] V. Lenhossék, *Verhandl. d. anat. Kongresses in Halle*, 1902. See *Centralbl. f. Gynäk.*, 1904, Nr. 7.

[2] Bonnet, "Über Syncytien, etc.," *Monatsschr. f. Geburtsh. u. Gynäk.*, vol. xviii., 1903.

[3] Graf v. Spee, "Neue Beobachtungen über sehr frühe Entwickelungsstufen des menschlichen Eies," *Arch. f. Anat. u. Phys.*, Anat. Abth., 1896.

There is a third theory regarding the transmission of nutritive material from the mother to the fœtus, viz. by the actual passage of maternal leucocytes, charged with nutriment, from the one circulation to the other. This theory was first advocated by Rauber[4] as the result of microscopic investigations, and he instanced, as further

[1] His, "Die Umschliessung der menschl. Frucht während der frühesten Zeit der Schwangerschaft," *Arch. f. Anat. u. Phys.*, Anat. Abth., 1897.

[2] Strahl, "Der Bau der Hundeplacenta," *Arch. f. Anat. u. Phys.*, Anat. Abth., 1890.

[3] Heinricius, "Ueber die Entwicklung und Struktur der Placenta beim Hunde," *Arch. f. mikr. Anat.*, vol. xxxiii., 1889.

[4] Rauber, *Ueber den Ursprung der Milch und die Ernährung der Frucht im allgemeinen*, Leipzig, 1879. Also *Zool. Anz.*, No. 70.

evidence in its favour, the greater number of leucocytes in the blood of the umbilical vein than in that of the artery. This view, which explained satisfactorily the passage of non-diffusible materials, subsequently received wide support. Thus Wiener[1] said: "It may be held as nearly without doubt that leucocytes cross from the maternal to the fœtal blood," and Preyer[2] considered the passage of leucocytes "indisputable." The first objection was raised in a paper by Paterson.[3] In it he recorded three cases of pregnancy complicated by leucocythæmia in the mother, and stated that the infants appeared quite normal and healthy, and their blood was of the usual colour and not white like the mothers'. These results were corroborated in similar cases by Cameron[4] and Sänger,[5] who actually counted the fœtal leucocytes and found no increase. More recently, Spire and Perrin,[6] in a case where the mother had pernicious anæmia, found that the fœtal blood was practically normal. These observations, and the inability of other investigators to demonstrate healthy leucocytes in the tissues intervening between the maternal and fœtal blood, have led to the abandonment of Rauber's theory.

But though maternal leucocytes do not pass as such straight into the fœtal blood, they may be important in another way. In Ruminants, Bonnet[7] has drawn attention to the enormous number of degenerated leucocytes in the uterine milk, and demonstrated their absorption by the ectoderm, and similar observations have been recorded in Carnivores. In these orders leucocytes undoubtedly form a part of the embryonic nutriment. In the rest of the deciduate Mammals they seem to play a less important part.

III. The Decidua

In the uterine mucosa during pregnancy the most noticeable change occurs in the interglandular tissue of discoid placentæ, in which *decidual* cells are formed. Various opinions have been held regarding their origin. Langhans, Hennig,[8] and others held that they were enlarged and modified leucocytes, but they could not support their theory by direct observation. Overlach[1] and Frommel[2] described them as modified glandular cells, but there is no doubt that the true origin is, as Creighton[3] first suggested, from the interglandular tissue of the mucosa. This consists of connective tissue of an embryonic type, which allows of a rapid transformation of its cellular elements. Masquelin and Swaen[4] demonstrated this mode of origin in Rodents, and were supported by Minot, and Hart and Gulland.[5] Leopold's studies of early ova showed that the same origin was most probable in man, and Peters described in the mucosa next the ovum connective tissue cells undergoing a decidual transformation.[6] Their first appearance in the superficial layers of the mucosa has suggested a stimulus for their formation arising from the product of conception.[7] The study of early human specimens has effectually disproved Ercolani's[8] idea that the uterine mucosa was first entirely destroyed by the developing ovum, and then replaced by decidual tissue formed from the cells of the vessel-walls. Such an endothelial proliferation does, however, occur in certain animals, *e.g.* hedgehog (Hubrecht[9]) and bat (Nolf[10]), and probably in ectopic gestation in man.

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[1] Wiener, "Die Ernährung des Fötus," *Samml. Klin. Vorträge*, No. 290.

[2] Preyer, *Specielle Physiologie des Embryo*, 1883.

[3] Paterson, "Cases of Acute Leucocythæmia in connection with Pregnancy," *Edinburgh Med. Jour.*, 1870.

[4] Cameron, "The Influence of Leucæmia upon Pregnancy," *Internat. Jour. of the Med. Sc.*, 1888.

[5] Sänger, "Ueber Leukämie bei Schwangeren und angeborene Leukämie," *Arch. f. Gynäk.*, vol. xxxiii., 1888.

[6] Spire and Perrin, "Un Cas d'Anémie pernicieuse de la Grossesse," *Bull. de la Soc. d'Obstet. et de Gyn. de Paris*, (Nov.) 1912.

[7] Bonnet, "Über Embryotrophe," *Deuts. med. Woch.*, 1899.

[8] Hennig, *Studien über den Bau der menschlichen Placenta, etc.*, Leipzig, 1872.

The rapid increase in the size and number of the decidual cells, together with the dilatation of the blood-vessels, leads to a great increase in the thickness of the serotina. At a certain stage it reaches its full development, and then gradually diminishes till, at the end of gestation, it forms only a thin layer, and even disappears entirely at parts so that the villi impinge on the muscular wall.

Individual decidual cells have probably a short life-history. Even at a comparatively early period many of them are found in various stages of hyaline degeneration, giving rise in part to the layers of fibrin, and as pregnancy advances there is a gradual extension of the fibrinous change. The degeneration of the decidual tissue would seem to be due to the influence of the fœtal epiblast, as in man it occurs much earlier and more abundantly in the serotina and reflexa than in the vera (Webster[1]). Its gradual diminution during pregnancy indicates an absorption of the decidua. That maternal tissues do not play a large part in this absorption is probable from the small number of leucocytes and the absence of lymph-channels in the neighbourhood of the fibrinous masses. At the same time, specialised decidual cells, which have the power of destroying the rest of the decidual tissue, have been described in the hedgehog,[2] rat, and other animals. But it is now generally accepted that the fœtal ectoderm from the earliest stages of pregnancy is able to disintegrate the cells with which it comes in contact, and to absorb the degenerate products. To that part of the fœtal epiblast which is thus adapted for the acquirement of embryonic nutriment the name of *trophoblast* has been given by Hubrecht. It forms the outer or ectodermal layer of the false amnion or chorion (see below, p. 412).

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[1] Overlach, "Die pseudomenstruirende Mucosa Uteri nach akuter Phosphorvergiftung," *Arch. f. mikr. Anat.*, vol. xxxv., 1885.

[2] Frommel, "Beitrag zur Frage der Wachstumsrichtung der Placenta," *Zeitsch. f. Geburtsh. u. Gynäk.*, vol. xxxvi.

[3] Creighton, "The Formation of the Placenta in the Guinea-pig," *Jour. of Anat. and Phys.*, vol. xii., 1878.

[4] Masquelin and Swaen, "Premières phases du développement du placenta chez le lapin," *Bull. de l'Acad. roy. de Belg.*, 1879.

[5] Hart and Gulland, "On the Structure of the Human Placenta, etc.," *Labor. Rep., Roy. Coll. Phys.*, Edinburgh, vol. iv., 1892.

[6] *Cf.* Ulesko-Stroganoff, "Zur Frage von dem feinsten Bau des Deciduagewebes, etc.," *Arch. f. Gynäk.*, vol. lxxxvi., 1908.

[7] Under abnormal conditions the formation of decidual cells occurs even although no ovum is present in the uterus, *e.g.* in tubal pregnancy in the human female. This indicates a chemical stimulus, probably from the corpus luteum, effected through the blood-stream (see p. 368). Moreover, it is known that decidual tissue is formed as a result of artificial or mechanical stimuli, provided that an active corpus luteum is present in the ovary (see p. 374).

[8] Ercolani, "Sulla unita del tipo anatomico della placenta," *Mem. dell' Accad. di Bologna*, 1876.

[9] Hubrecht, "The Placentation of *Erinaceus europæus*," *Quar. Jour. Micr. Science*, vol. xxx., 1889.

[10] Nolf, "Modifications de la muqueuse utérine pendant la gestation chez le murin," *Arch. de Biol.*, vol. xiv., 1896.

Along with the gradual absorption of the degenerated parts of the decidua, and the great increase in the extent of the serotinal surface as pregnancy advances, there is probably a continued formation of new decidual elements. Pfannenstiel attributes the new formation to the perivascular tissue, and Webster to groups of active cells, the "Ersatz-zellen" of Klein,[3] found here and there in the mucosa. Whatever their origin is, we may see, even in the shed placenta at full time, well-formed and apparently healthy decidual elements as well as the fibrinous masses containing cellular fragments.

Within recent years there has been a tendency to belittle the importance of the connective tissue elements of the placenta. This has been largely due to the wider acceptance of the fœtal origin of the syncytium, and to the conception of the placenta as a maternal hæmorrhage circumscribed by fœtal structures. But the same idea has been encouraged by some who look on the syncytium as maternal, and they adduce as evidence the obvious degeneration in the decidua during the greater part of pregnancy. Pfannenstiel maintains that decidual cells are, from the beginning, degeneration forms of the connective tissue cells and are of use only as pabulum to be absorbed by the ovum. But during the whole of pregnancy, as mentioned above, there exist in the placenta decidual cells which, in their appearance and staining properties, show no resemblance to degenerated cells. From their abundance and great specialisation they have in all likelihood definite functions to perform. Their first formation dates from the destruction of the surface epithelium when the blastocyst comes in contact with the connective tissue, and the earliest to appear are in the neighbourhood of the ovum. Their position and general appearance in different orders suggested to Turner a maternal reaction against the advance of the parasitic ovum, and the same idea has been forced on different observers. Fothergill[1] speaks of the decidua preventing the injurious invasion of the uterine wall by the fœtal elements. Chipman's[2] figures of the placenta of the rabbit show that the ectoplacenta advances more rapidly where it encounters a vessel than where it lies against decidual cells. Wade and Watson[3] have noted its resemblance to young granulation tissue in the mucosa of the Fallopian tube in an early ectopic pregnancy. Bryce and Teacher,[4] in their description of the youngest human ovum yet examined, say: "The decidua formation is a process of a conservative nature, by which, during the early months of pregnancy, the activities of the trophoblast are limited and controlled until such time as placentation is complete." Whether or not the decidua forms the protection to the mother, there is increasing evidence that the trophoblast does not invade the decidua to the extent supposed by the older authorities. This was first emphasised by Hubrecht in the hedgehog, and has more recently been advocated by Webster, and by Bryce and Teacher, in man.

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[1] Webster, *Human Placentation*, Chicago, 1901.

[2] In a later memoir Hubrecht assigns to these cells, the deciduofracts of the hedgehog, an origin from the outer layer of the trophoblast. See footnote, p. 496.

[3] Klein, "Entwicklung und Rückbildung d. Decidua," *Zeitsch. f. Geburtsh. u. Gynäk.*, vol. xxii.

Hoffmann[5] and Ahlfeld[6] considered the decidua to be of the nature of a diffuse gland whose cells secreted a nutritive juice for the wants of the fœtus. They stated that they could demonstrate such a secretion in the "intervillous" spaces formed by the separation of the decidual cells; but their observations have been discounted by the investigations of Werth,[7] who showed that the spherical globules described by Hoffmann were never present in the fresh placenta, but

[1] Fothergill, "Decidual Cells," *Edin. Med. Jour.*, vol. v., 1899.

[2] Chipman, "Observations on the Placenta of the Rabbit, etc.," *Edin. Roy. Coll. Phys. Labor. Rep.*, vol. viii., 1903.

[3] Wade and Watson (B. P.), "The Anatomy and Histology of an Early Tubal Gestation," *Jour. of Obstet. and Gynec. of the Brit. Emp.*, 1908.

[4] Bryce and Teacher, *Contributions to the Study of the Early Development and Imbedding of the Human Ovum*, Glasgow, 1908.

[5] Hoffmann, "Sicherer Nachweis der sogenannten Uterinmilch beim Menschen," *Zeitsch. f. Geburtsh. u. Gynäk.*, vol. viii., 1882.

[6] Ahlfeld, *Berichte u. Arbeiten aus der geburtsh. Klinik zu Giessen*, Leipzig, 1883.

[7] Werth, "Beiträge zur Anatomie, Physiologie, und Pathologie der menschlichen Schwangerschaft," *Arch. f. Gynäk.*, vol. xxii.

appeared only after its separation, and probably consisted of droplets exuded by the dying chorionic epithelium. It may be mentioned here that the "boules," described by Nattan-Larrier[1] as an internal secretion of the syncytium, have been thought by many to be a post-mortem appearance.

In Rodents the decidual cells have an important and definite part to play in synthesising and storing glycogen as a supply of carbohydrate for the fœtus. In man also the decidual cells contain glycogen at an early period. Fat globules infiltrate the decidual cells of various animals at a stage when there is no question of a fatty *degeneration* taking place in the cells. Finally, the cells appear to have the power of ingesting and decomposing erythrocytes, but their relations to the iron-metabolism of the fœtus require further study.

PART II

THE FIRST STAGES OF PREGNANCY: PLACENTAL CLASSIFICATION

I. The Ovarian Ovum

While still in the ovary, the ovum obtains the necessary nutriment by means not yet discovered. In the Graafian follicle it is surrounded by the zona pellucida and externally the corona radiata.[2] The origin of the zona pellucida has been variously described. According to some authorities it is the thickened outer edge of the ovum itself, a true vitelline membrane, but it is more probably a deposit from the cells of the corona radiata. Its structure is almost homogeneous, but with the highest powers of the microscope fine striæ are seen running from without inwards. Their appearance indicates the possibility that they are pores or delicate canals by which protoplasmic processes of the cells of the corona radiata, or a secretion of these cells, may reach the ovum and nourish it (see p. 121). Whatever the source of the food-supply of the ovum is, it not only increases in size until it is ripe for deliverance, but stores in its protoplasm yolk granules, the *deutoplasm* of Beneden, which increase in number as the ovum approaches maturity. The granules vary in size and number in different species, and also in their position. They may be mingled uniformly through the cytoplasm, or be collected at the marginal zone (sheep), or at the periphery of the central zone (man). During the earliest stages of segmentation, when perhaps food is not readily accessible, or a specialised form of nutriment is required, the granules are used up.

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[1] Nattan-Larrier, "Fonction sécrétoire du placenta," *Comp. Rend. de l'Acad. de Sc.*, vol. lii., 1900.

[2] Or zona radiata, *i.e.* the innermost layer of follicular epithelium and within the discus proligerus.

II. THE FERTILISED OVUM AND ITS COVERINGS

When the ovum leaves the ovary it carries with it the zona pellucida and cells of the corona radiata. After fertilisation, which most probably occurs in all animals at the outer end of the oviduct or Fallopian tube, the cells disappear and are replaced in some species by a homogeneous sticky layer of albuminous material. According to Robinson,[1] it is derived in part from the disintegrated cells of the corona radiata, but most of it seems to be obtained from the secretion of the tubal and later of the uterine glands.[2] It is covered by villous tufts, which led to its designation as *prochorion* by Henson. But the tufts are merely casts of the gland-ducts, due to the coagulation of the secretion by the use of reagents.

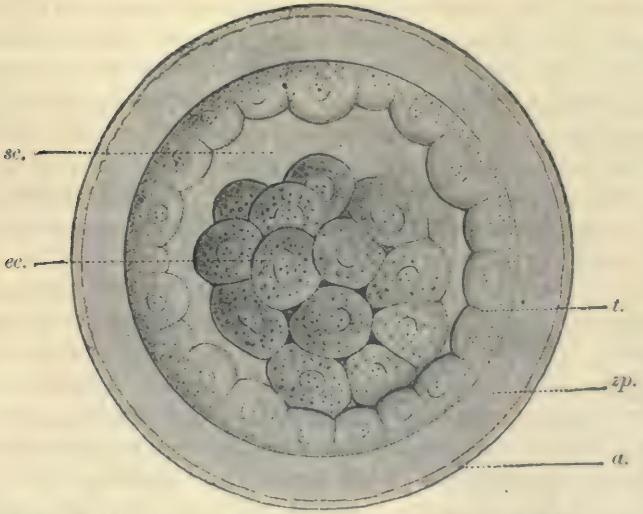

FIG. 99.—Early blastocyst of the rabbit. (From Hertwig's *Entwicklungsgeschichte des Menschen und der Wirbelthiere.* By permission of Gustav Fischer.)

a, Albumen layer ; *zp*, zona pellucida ; *t*, trophoblast ; *sc*, segmentation cavity ; *ec*, mass of embryo cells.

The investment formed by the two layers around the ovum is very thick in Marsupials. In Ungulates it forms a thin coat, which disappears at a comparatively early stage in the pig, sheep, and deer. In the last named, according to Bischoff, there is no albumen layer. In Carnivores there is invariably a firm coat of zona pellucida or albumen layer, or both, which persists, in the dog and ferret at least, till the appearance of the primitive streak and the commencement of the formation of the mesoderm (Robinson). In Rodents there are differences. In the rabbit (Fig. 99) the albuminous layer is well marked while the fertilised ovum is still in the Fallopian tube; on the fourth day, when the uterus is reached, it rapidly thins but remains up to the eighth day (Assheton[1]). In the rat the covering disappears early—usually about the eight-cell stage. In the mole the covering is thick, and, according to Heape,[2] the albumen layer is applied in the uterus and not in the Fallopian tube. It persists, as in the shrew, till the embryonic ectoderm appears on the surface of the ovum. In the hedgehog and bat it disappears before the blastocyst is formed, and in *Tupaia javanica* it may be already absent in the two-cell stage. Little is known of it in the Primates; in the earliest ovum investigated, the four-cell stage of *Macacus nemestrinus*, it had already disappeared.

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[1] Robinson, "On the Early Stages of Development of Mammalian Ova, and on the Formation of the Placenta," Hunterian Lectures, *Jour. of Anat. and Phys.*, vol. xxxviii., 1904.

[2] Bonnet, "Ueber das Prochorion der Hundekeimblase," *Anat. Anz.*, vol. xiii., 1897.

With regard to its functions, there is little doubt that the degenerating cells of the corona radiata, and later the albumen layer, serve as food for the growing mass of the ovum in the Fallopian tube and uterus. In the investment in the mouse, Jenkinson[3] found nutritive substances—fat, and probably also protein matter. In addition, Bonnet has adduced strong evidence to show that it is absorbed by the ectoderm of the blastodermic vesicle. In the rabbit the albumen layer forms a tough, strong membrane enclosing at the end of the third day the solid morula. Within the mass of cells a cavity develops and rapidly increases by diffusion inwards of fluid. "It is hardly conceivable that the delicate cells could cause expansion of the tough albuminous wall. Rather the osmotic current is more inwards than outwards, either simple or more probably assisted by the vital activity of the cells" (Assheton). Heape had previously pointed out that the increasing fluid must be secreted into the interior of the blastocyst under considerable pressure, as the vesicle remains spherical and extends the uterine walls before it. Once inside, the fluid exerts a greater or less hydrostatic pressure, which is counteracted by the albumen layer, and the rupture of the vesicle is prevented. At the beginning of the cavity-formation in the morula, the cells are not yet pressed on by the investment. Later the vesicle increases in size, and the outer cells are pressed and flattened. At the same time the albumen layer is thinned, and is soon hardly perceptible. Finally it ruptures, and immediately afterwards the blastodermic vesicle is flaccid, apparently from injury to its wall.

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[1] Assheton, "The Attachment of the Mammalian Embryo to the Walls of the Uterus," *Quar. Jour. Micr. Science*, vol. xxxvii., 1895.

[2] Heape, "The Development of the Mole (*Talpa europæa*), etc.," *Quar. Jour. Micr. Science*, vol. xxiii., 1883.

[3] Jenkinson, "Observations on the Physiology and Histology of the Placenta of the Mouse," *Tijd. Nederl. Dierk.*, Ver. ii., Dl. 7.

Besides its nutritive and protective function, the investing layer may prevent the contact of the external cells of the blastodermic vesicle with the cells of the uterus. Only when it has disappeared is fusion of the maternal and fœtal elements possible. Robinson has followed out this idea in different Mammals. He suggests that in those animals (Carnivores, rabbit) in which the embryonic ectoderm reaches the surface, the albumen layer prevents contact with the uterine wall till differentiation of the ectodermal cells has taken place to such an extent that they are no longer disposed to fuse with the uterine tissues. In those in which the embryonic ectoderm never reaches the surface (mouse, guinea-pig, hedgehog, bat, probably Primates), the investment disappears before the blastula is attained.

With the disappearance of the zona, the developing ovum lies naked in the Fallopian tube or the uterus. It takes some time to complete the journey along the tube—about eighty hours in the rabbit, and a little longer in the sheep; in the guinea-pig it is said to reach the uterus on the seventh day after copulation and while in the morula stage.[1] For a further period it remains unattached in the uterine cavity, and then, by processes which vary in different orders, it obtains attachment—loose in Marsupials and firmer in the other orders. Peters[2] has described a human ovum of five or six days when the decidua was still undergoing differentiation. The ovum was sunk in it but was not as yet completely covered. Leopold[3] in a uterus removed surgically for cervical cancer found a seven days' ovum entirely enclosed by the decidua.

At first each blastomere is nourished separately; but when the blastocyst is formed, the greater part of its outer layer is set aside to look after the nutrition of the whole, and takes no share in the formation of the embryo or amnion. To that part Hubrecht gave the name of *trophoblast*,[4] and the term has been generally accepted. Already, before the embryo is elaborated, provision is in this way made for its maintenance.

III. THE UTERINE MUCOSA

While the ovum is still in the oviduct, no obvious changes occur in the uterus itself. In the sheep, Assheton,[1] detected no difference except an increase in the number of the leucocytes. There was no sign of activity in the uterine glands or blood-vessels. When the ovum reaches the uterus changes begin—dilatation of blood-vessels and lymphatics, widening and increased tortuosity of glands, disappearance of cilia from the surface epithelium. The whole mucosa is soft and œdematous, and there may even be a transudation of lymph entering the uterine cavity and mingling with the glandular secretion to form a supply of nutriment for the ovum before attachment. Great differences, however, occur, and it is more convenient to describe the changes in the uterine mucosa in each order.

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[1] Von Spee, "Die Implantation des Meerschweincheneies in die Uteruswand," *Zeitsch. f. Morph. und Anthropol.*, vol. iii., 1901.

[2] Peters, *Über die Einbettung des Menschlichen Eies*, Leipzig und Wien, 1899.

[3] Leopold, *Uterus und Kind*, Leipzig, 1897.

[4] See below, p. 412.

IV. Placental Classification

At the outset we are beset with the difficulty of grouping Mammals in such a way as to show how the variations in the anatomy and physiology of the placenta have been evolved. Well-marked differences, such as occur in other organs and serve to differentiate Mammals into certain orders, are not always to be observed in their placentæ. In widely diverging groups there may be striking similarities in placentation, while great differences may exist in closely related types. On this account the most satisfactory, and indeed the only possible, classification of Mammals for our purpose is one based on their placental characters. Such a classification was introduced by Huxley[2] in 1864. He divided Mammals into two great sections according as their placentæ were *non-deciduate* or *deciduate*.[3] In Deciduates the substance of the mucosa undergoes rapid growth and textural modification to form decidual tissue, and the maternal and fœtal parts of the placenta become firmly united. In Non-deciduates there is no formation of decidual tissue, and at parturition the fœtal villi are simply drawn out like the fingers from a glove, no vascular substance from the mother being thrown off.

In a later publication[4] Huxley attempted to arrange all Mammals in one or other division. The Deciduata are classed in two groups according to the external appearance of the placenta, which is either *zonary*,[5] as in Carnivora and Proboscidea; or *discoid*, as in Rodentia, Insectivora, Cheiroptera, Lemuridæ, Simiidæ, and Primates. The Non-deciduata are the Ungulata and Cetacea. The Sirenia and

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[1] Assheton, "The Morphology of the Ungulate Placenta, etc.," *Phil. Trans. Roy. Soc.*, London, Ser. B., vol. cxcviii., 1906.

[2] Huxley, *The Elements of Comparative Anatomy*, London.

[3] Thirty years earlier Weber had suggested a similar division into *caducous* and *non-caducous*; but his terms, although accepted by von Baer and Eschricht, were displaced by those of Huxley.

[4] Huxley, *Introduction to the Classification of Mammals*, London, 1869.

[5] When the chorionic villi are limited to an annular area the placenta is called zonary.

Edentata offer difficulties. Of the latter, *Manis* has a diffuse placenta, *Bradypus* a poly-cotyledonary, and *Orycteropus* a zonary and deciduate placenta. One of the Sirenia, the dugong, which possesses a zonary but not deciduate placenta, illustrates a type not represented at all in Huxley's classification. No maternal tissue is lost at birth; but, in addition, part of the fœtal tissue remains attached to the uterus and is absorbed (Turner[1]). The placenta of the mole is not shed at birth, but becomes gradually absorbed by the mother. For such Hubrecht[2] suggested the term *contra-deciduate.*

The classification of Strahl[3] does not promise to be any more satisfactory. He divides Mammals into two groups, one having a "Halbplacenta" and the other a "Vollplacenta." In the former no maternal vessels are opened and the connection is less intimate, while in the latter hæmorrhages occur during pregnancy. But in a physiological sense the *half* placenta is certainly as efficient an organ of nutrition as the *whole* placenta.

In view of the more recent work on the placenta, it is obvious that Huxley's classification fails in taking no account of the trophoblast, the most active constituent of the placenta, and in laying too much stress on the differences at birth, *i.e.* on the shedding of an organ which is of no more use, and may be considered as physiologically dead. Moreover, it would appear that in many of the deciduate Mammals almost no maternal tissue except blood is lost at birth, and maternal blood is also lost in the non-deciduate sheep. A perfect classification must take account of the structure and behaviour of the trophoblast during the whole course, or at least the earlier part, of pregnancy. Without it a clear insight into the processes which regulate fœtal nutrition cannot be obtained. Robinson[4] and Assheton[5] have made efforts in this direction, the former emphasising the methods of attachment of the trophoblast to the uterus, and the latter the anatomical condition of the trophoblast at the time of its first attachment. Hubrecht, on the basis of Huxley's statement that Insectivora are among the most archaic of Mammals, has investigated several members of this order as showing probably the most ancient type of placenta, and thus affording a starting-point for a classification. According to Huxley, the least differentiated types, the hedgehogs and *Gymnura*, occupy a central position, while shrews show resemblances to Rodents, and *Tupaia* to lemurs; moles and *Galeopitheci* vary in other directions, while the whole order shows more general relationships to Carnivores and Ungulates. But at present these relationships are not understood. It seems impossible to trace any connection between the placenta of the sheep, in which there is no circulation of maternal blood in the fœtal parts of the placenta but the fœtus is nourished by *uterine milk*, and that of the hedgehog, in which maternal blood circulates in the trophoblastic lacunæ and forms the main source of nutriment.

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[1] Turner, "On the Placentation of *Halicore dugong*," *Trans. Roy. Soc. Edin.*, vol. xxxv., 1889.

[2] Hubrecht, "Spolia Nemoris," *Quar. Jour. Micr. Science*, vol. xxxvi., 1894.

[3] See Hertwig, *Entwicklungsgeschichte des Menschen und der Wirbelthiere*, 1906.

[4] Robinson, Hunterian Lectures, *loc. cit.*

[5] Assheton, "The Morphology of the Ungulate Placenta," *Phil. Trans. Roy. Soc.*, London, Ser. B., vol. cxcviii., 1906.

Hubrecht[1] has contributed an important memoir setting out in some detail his views on the phylogeny of the placenta and its classificatory value, and Assheton[2] has expressed himself as in agreement with the general trend of Hubrecht's ideas. According to these authorities we have on the one hand in the Ungulata, Sirenia, Cetacea, and some Edentata a great lateral expansion of the trophoblast, leading to the "plicate" type of placenta, and on the other hand in Insectivora, Cheiroptera, and Primates cell proliferation of the trophoblast producing thickenings thereof and leading to the "cumulate" type of placenta. The differences between the two types are summarised by Assheton as follows:—

Cumulate Placenta.	Plicate Placenta.
Great radial proliferation of trophoblast, leading to thickening of the membrane.	Great tangential proliferation of trophoblast, leading to folding of the membrane.
Greater destruction of maternal tissue.	Lesser destruction of maternal tissue.
Much bleeding of mother.	Little bleeding of mother.
Lacunisation of trophoblast.	No lacunisation of trophoblast.
Secretion of uterine glands of less use, or in some cases of no use, to the fœtus.	Secretion of uterine glands of prime importance.
Degeneration of uterine epithelium and glands severe.	Little or no degeneration of uterine epithelium and glands.
Embryo or embryos seldom fill the whole cavity of the uterus.	Embryo or embryos usually fill the whole cavity of the uterus.

According to Assheton the reason for the causation of the latter character is that "fixation is brought about or other intimate connection in the cumulate type, while fixation in the plicate type depends more upon the internal hydrostatic pressure of the blastocyst upagainst the uterus—much as a pneumatic tyre retains its position in the iron rim of a bicycle wheel."

The Carnivora are regarded as a central group with respect to placentation from which either cumulate or plicate type could be evolved. In this connection it may be recalled that in the œstrous cycle of the dog there is a normal pseudo-pregnant period in the absence of gestation, and that this is to be regarded as a primitive characteristic.

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[1] Hubrecht, "Early Ontogenetic Phenomena in Mammals," *Quar. Jour. Micr. Science*, vol. liii., 1908.

[2] Assheton, "Professor Hubrecht's Paper, etc.," *Quar. Jour. Micr. Science*, vol. liv., 1909.

Hubrecht considers the extreme cumulate placenta to be more primitive than the extreme plicate one, but his view is based on the assumption of a non-Sauropsidan origin of Mammals with which Assheton is unable to agree. The Lemurs are described by Assheton as "pseudo-plicate," having been derived separately from Mammals with a cumulate placenta. The Marsupials are regarded as being specialised descendants of placental Mammals (Hubrecht).[1]

In this chapter we must be content with a review of the processes occurring in several Mammals which have been more particularly investigated, without straining to find how such processes have arisen in the course of placental evolution. The arrangement of the mammalian orders is more in accordance with the older views of placental classification, but nevertheless an attempt has been made to emphasise the trophoblastic characteristics.

PART III

THE FŒTAL MEMBRANES, THE YOLK-SAC, AND THE PLACENTA

I. General Anatomy of the Fœtal Membranes

So far no reference has been made to the part played by the mesoblast in the nutrition of the embryo. The placenta has been described as an organ consisting of maternal and fœtal elements—of modified uterine mucosa, and trophoblast which absorbs nutritive material from the mucosa and from the maternal blood. The nutriment serves in part for the nutrition of the trophoblast itself, and in part for the growth and development of the embryo. In the earliest stages there are as yet no embryonic vessels, and the nutriment is transmitted from cell to cell. But as the embryo increases in size and its requirements grow in proportion, such a path becomes inadequate, and a vascular channel is developed in connection with the two fœtal membranes—the *yolk-sac* or umbilical vesicle, and the *allantois*.

The mammalian yolk-sac has only a secondary importance for the nutrition of the embryo. The blastodermic vesicle at an early stage of development is divided into an embryonic and a non-embryonic area. The latter is the yolk-sac which gradually becomes folded off from the embryo. Its relations are the same as those of the yolk-sac in Sauropsida, but the contents are an albuminous fluid instead of yolk. It is commonly believed that the placental Mammals are descended from ancestors in which the ovum had a large supply of yolk, but that, when the fertilised ovum found a new supply of food in the uterus, the yolk was reduced and ultimately disappeared. At the same time the envelopes, which were developed under the influence of the vitelline contents, have been preserved and modified in different ways to aid uterine nutrition.[1]

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[1] See also Hubrecht, "Is the Trophoblast of Hypoblastic Origin, as Assheton will have it?" and "The Fœtal Membranes of the Vertebrates," *Quar. Jour. Micr. Science*, vol. lv., 1910.

In the early stages the development proceeds, as in birds and reptiles, with the gradual extension of the hypoblast round the wall of the blastocyst, which thus becomes *didermic.* The mesoblast grows out between the epiblast and hypoblast, starting at the embryonic area and gradually extending for a variable distance round the wall of the blastocyst. Near the embryo appears the *area vasculosa,* in which blood-vessels and blood are developed from the cells of the mesoblast, while at the same time the embryo begins to be folded off from the yolk-sac by anterior and posterior folds. The area gradually extends further and further round. Its outer boundary is marked by the *sinus terminalis* which communicates with the vitelline veins. The blood is brought from the dorsal aortæ by a series of lateral vitelline branches. These arteries break up into a deeper arterial network, from which the blood is collected into the sinus terminalis and the superficial venous network, and in this way reaches the vitelline veins and so passes to the heart.

During the spread of the mesoblast, it splits into an external layer or *somatopleur,* and an internal layer or *splanchnopleur.* The former is non-vascular and adheres to the inner aspect of the trophoblast which is ectodermal, forming with it the *diplo-trophoblast,* otherwise called the false amnion or chorion, and the splanchnopleur is applied externally to the hypoblastic wall of the yolk-sac. By the splitting a space is formed between the two layers. This is the *extra-embryonic cœlom,* which thus intervenes over a larger or smaller area between the diplo-trophoblast and the yolk-sac.

The amnion in the rabbit arises by the formation of folds of extra-embryonic ectoderm, together with the somatopleur which is in conjunction with it, the yolk-sac and the splanchnopleur taking no part in the process.[2] The extra-embryonic cœlom is continued into the folds, each of which contains two layers. The folds grow up over the dorsal surface of the embryo and eventually meet and fuse, and when the union is complete the outer and inner layers

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[1] According to Hubrecht's views, the mammalian ovum is not descended from the ovum of Sauropsida.

[2] In the guinea-pig and many other species of Mammals, including probably man, the amniotic cavity develops as a closed sac from its inception. It is formed inside the embryonic knot, which comprises the material for both amnion and embryo. For an account of the various ways in which the fœtal membranes are formed in the different animals see Jenkinson, *Vertebrate Embryology,* Oxford, 1913 (see below, footnote, p. 490).

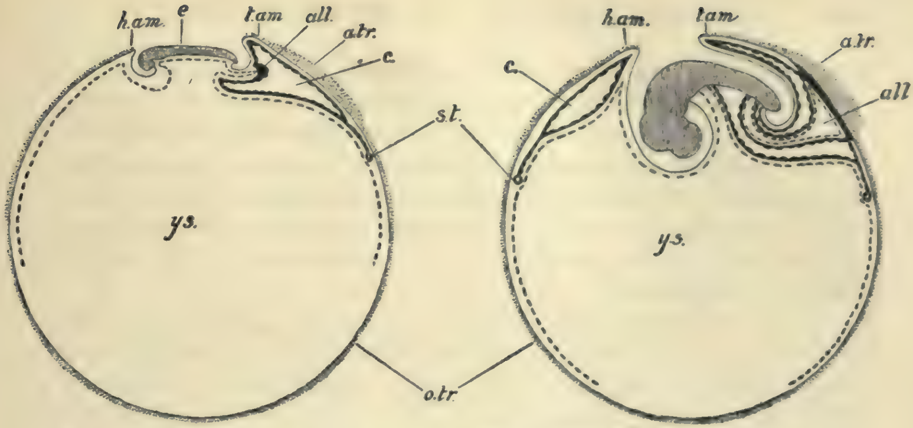

Fig. 100.—Formation of the amnion in the rabbit. (After van Beneden, from Jenkinson's *Vertebrate Embryology*, Oxford, at the Clarendon Press.)

h.am, Head amnion fold ; *t.am*, tail amnion fold ; *e*, embryo ; *all*, allantois ; *a.tr*, allantoidean trophoblast ; *y.s*, yolk-sac ; *o.tr*, omphaloidean trophoblast : *c*, extra-embryonic cœlom ; *s.t*, sinus terminalis of area vasculosa.

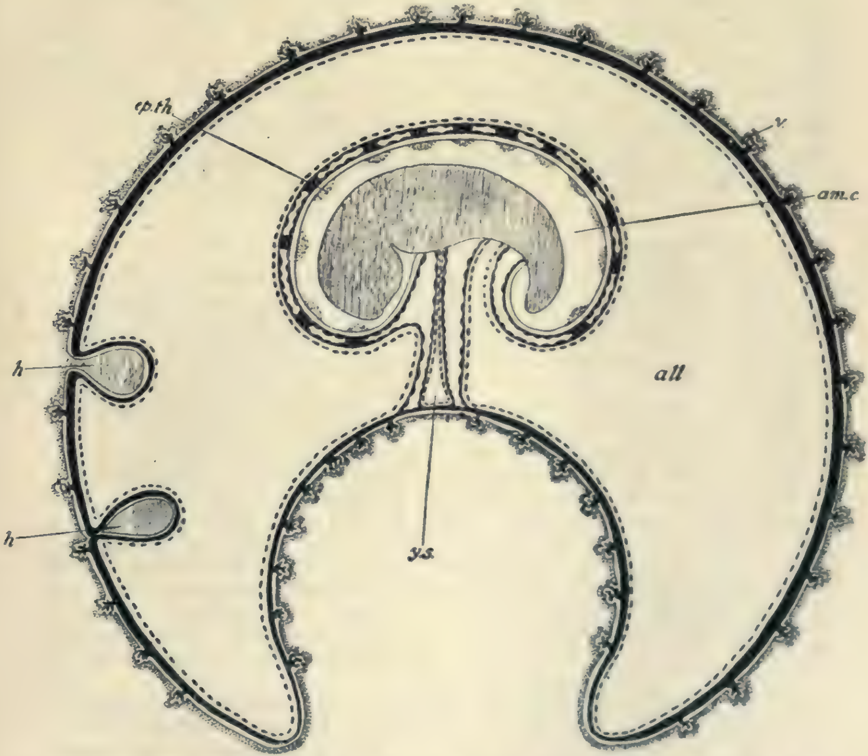

Fig. 101.—Fœtal membranes of horse, later stage. (After Bonnet, from Jenkinson's *Vertebrate Embryology*, Oxford, at the Clarendon Press.)

v, Villus ; *ep.th*, epithelial thickenings of amnion ; *h*, hippomanes ; *am.c*, amniotic cavity ; *all*, allantois ; *y.s*, yolk-sac.

(each of which is composed of ectoderm and somatopleur) are separated by the cœlom. The outer layer becomes the false amnion or chorion,[1] and the inner layer the true amnion. Within the latter and immediately surrounding the embryo is the liquor amnii. This fluid protects the embryo from injuries and changes of temperature besides affording freedom of movement: moreover, it acts as a dilating wedge during parturition. It supplies water to the embryo but not nourishment.[2]

While the changes above described are taking place, the allantois grows out (on the tenth day in the rabbit) from the hind-gut as a vesicle lined by hypoblast, and covered externally by a layer of splanchnopleur.[3] In some Mammals the cavity of the allantois is not continued beyond the body-wall of the embryo, the extra-embryonic portion consisting of a solid rod of mesoblast. In all orders below the Primates, however, it projects free for a time into the cœlom, and later fuses, except in the Marsupials, with the whole or part of the outer wall of the blastocyst. In the allantoic mesoblast many vessels are developed, and branches extend into the projections which form the cores of the villi. The blood is brought by two allantoic arteries continued from the terminal bifurcation of the dorsal aorta, and returned by one, or more rarely two, allantoic veins. "While the placenta is being developed, the folding off of the embryo from the yolk-sac becomes more complete, and the yolk-sac remains connected with the ileal region of the intestine by a narrow stalk, the vitelline duct. While the true splanchnic stalk of the yolk-sac is becoming narrow, a somatic stalk connecting the amnion with the walls of the embryo is also formed, and closely envelops the stalk both of the allantois and yolk-sac. The somatic stalk, together with its contents, is known as the umbilical cord" (Balfour[1]). The yolk-sac atrophies completely in some, but in others it is only removed at birth.

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[1] See p. 476, footnote [3], and p. 490.

[2] That the liquor amnii supplies water to the fœtus, according to Feldman, is shown by the fact that hair, epidermal scales, etc., have been found amid the intestinal contents of the newly born. On the other hand, a well-nourished fœtus may be found with almost complete absence of liquor amnii or with the œsophageal lumen occluded, and so preventing it from swallowing the fluid. The liquor amnii is slightly alkaline in reaction; it consists chiefly of water, but contains slight quantities of albumen, fats, and inorganic substances. Urea and creatinin have been found in it, indicating that it may receive products of excretion by the fœtal kidney; moreover, benzoic acid administered to a pregnant animal led to the appearance of hippuric acid in the liquor amnii. As evidence that the fluid is partly of maternal origin are the facts that potassium iodide, etc., given to the mother appears in the liquor amnii but not in the fœtal urine, and that sugar is present in the fluid if the mother has diabetes (see below, p. 463). Jenkinson, however (*Vertebrate Embryology*, Oxford, 1913), describes glucose as present normally in the liquor amnii of the cow, and says that it increases towards the end of pregnancy, while glycogen, stored up in the stratified epithelium on the inner surface of the amnion, at the same time diminishes. For further evidence see Feldman, *Principles of Ante-Natal and Post-Natal Child Physiology*, London, 1920.

[3] Morphologically, therefore, the allantois is an extra-embryonic bladder. The fluid has been found to contain glucose (·3 per cent.), albumen, mucin, magnesium, sodium and calcium phosphates, sodium chloride, sodium sulphate, and crystals of calcium oxalate, besides a yellow pigment, and allantoin, a substance chemically related to uric acid. It seems, therefore, that the allantois, besides its more important function in connection with the formation of the placenta, acts as a receptacle for fœtal excretory products. See Jenkinson, *loc. cit.*

II. The Nutritive Importance of the Yolk-Sac

When the blastodermic vesicle becomes adherent to, or sinks into, the uterine mucosa, the wall of the yolk-sac in some orders becomes intimately related to the uterine mucosa and is nourished by it. Even in the non-mammalian Vertebrata the latter condition has been observed. In the Lacertilia the yolk-sac absorbs nutriment from the uterus through the porous shell. In *Mustelus lævis* the embryos lie in a fluid derived from the surface secretion and a lymphoid transudate of the uterine mucosa. It passes through the porous shell to reach the yolk-sac (Brinkmann[2]). In *Seps chalcides*, a reptile, the insufficient supply of yolk is added to by a uterine secretion containing degenerated cells and blood derivatives, the outer layer of the blastocyst being distinctly phagocytic (Giacomini[3]). But in the Sauropsida no union takes place between the maternal tissues and the fœtal membranes, and so in one order of Mammals, the Ornithodelphia,[4] where the young develop outside the body. In all the other orders the wall of the yolk-sac comes into relation with the uterine wall over a greater or less area, depending on the extent to which the mesoblast, spreading round the wall of the blastocyst, splits into two layers. In the non-mammalian Vertebrates, the mesoblast and the cœlom extend completely round and the yolk-sac is entirely separated from the surface layer; so in the sheep and man. In others (*e.g.* the rabbit) the cœlom does not spread so far.

It still remains to consider the path by which the nutriment is conveyed to the embryo. In partial extension of the area vasculosa, the wall of the yolk-sac consists of three parts, each with different relations (see Fig. 102): (1) The non-vascular part, with a two-layered wall of epiblast and hypoblast; (2) the vascular part, where the mesoblast is unsplit, *e.g.* in the opossum—the mesoblast splits in its entire extent in the rabbit; (3) the part opposite the cœlom. In all three parts the trophoblast is bathed by the uterine secretion after the disappearance of the prochorion. In the non-vascular part it is probably transmitted through the hypoblast cells to the yolk-sac, whence, in turn, it reaches the embryo either by the vitelline vessels or the developing alimentary canal. In the vascular part the same may occur, or the nutriment may be conveyed to the embryo directly by the vessels of the area vasculosa. It is in this region that the fœtal circulation is brought close to the maternal, and gaseous exchanges may be effected. Opposite the cœlom the trophoblast is lined by a thin layer of non-vascular somatopleur, through which transference of material to the cœlomic cavity is possible. This part is subsequently connected with the embryo by the allantoic vessels. When the yolk-sac is entirely separated from the outer wall, nutritive substances may also be transmitted to the cœlomic cavity and then to the embryo or yolk-sac.

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[1] Balfour, *Comparative Embryology*, London, 1881.

[2] Brinkmann, "Histologie, Histogenese und Bedeutung der Mucosa Uteri einiger Viviparer Haie und Rochen," *Mitt. a. d. Zool. Stat. z. Neapel.*, vol. xvi., 1903.

[3] Giacomini, "Ueber die Entwicklung von Seps Chalcides," *Anat. Anz.*, vol. vi., 1891.

[4] Or Monotremata.

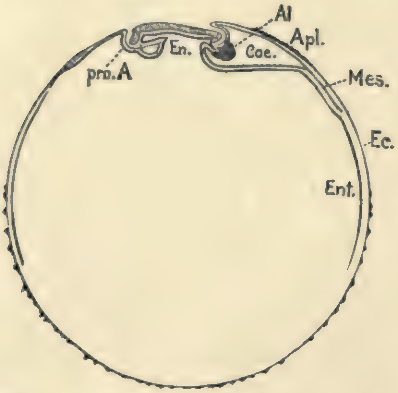

Fig. 102.—Diagram to illustrate the three parts of the wall of the yolk-sac in the rabbit. (From Minot's *Human Embryology*, by permission of William Wood & Co.)

Al, Allantois; *Apl*, area placentalis; *Ec*, ectoderm; *Mes*, mesoderm; *Ent*, extra-embryonic entoderm; *Cœ*, cœlom; *En*, entodermic cavity of the embryo; *pro.A*, proamnion.[1]

The nutritive importance of the yolk-sac may now be considered in greater detail in several orders of Mammals.

Marsupials.—In the opossum the mesoblast spreads about half-way round the wall of the blastocyst, but it does not split over its whole extent. Hence the cœlom is small, and correspondingly the separation of the yolk-sac and trophoblast is insignificant (Fig. 103). The allantois grows out into the cœlom only to impinge on and invaginate the wall of the yolk-sac. It never comes in contact with the outer wall of the blastocyst. The part of the wall where the mesoblast is unsplit is thrown into folds which fit into corresponding furrows of the mucosa. Hence an avillous yolk-sac placenta is formed (Selenka[2]). The nutrition in the uterus is very primitive. The ova contain a comparatively large supply of yolk granules for the initial stages of development. As they travel along the oviduct and into the uterus, they are invested with a thick nutritive layer, derived from the secretion of the tubal and uterine glands. Later the embryos are also nourished by the primitive placental structures for a period short in duration, but long enough to allow of the differentiation of their main organs and systems. In the mucosa the surface epithelium remains intact. The only change is an œdema of the layers, and the sole nutritive material is a watery fluid, composed of glandular secretion and a lymph transudate almost devoid of cells. It is absorbed by the trophoblast cells, which here and there enlarge to enormous "Nährzellen" and so increase the absorbing surface. After eight days the food supply becomes inadequate for the developing embryos, and they are transferred to the pouch and nourished by the mammary secretion.

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[1] The name proamnion is given to that region of the amnion below the head of the embryo from which the mesoderm is absent. In Marsupials this may persist.

[2] Selenka, *Studien über die Entwicklungsgeschichte der Thiere*, Wiesbaden.

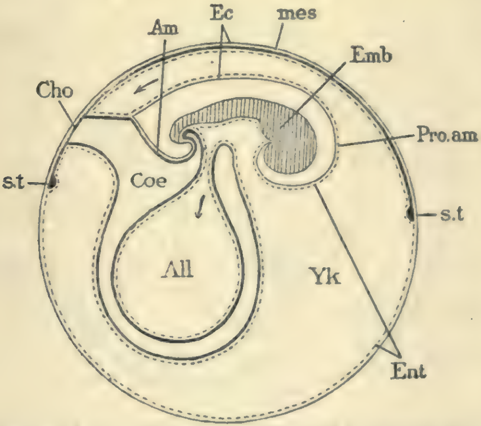

FIG. 103.—Diagram of an opossum embryo and its appendages. (From Minot.)

All, Allantois; *Yk*, cavity of yolk-sac; *Coe*, cœlom; *Am*, amnion; *Pro.am*, proamnion; *Emb*, embryo; *Ec*, ectoderm; *Ent*, entoderm; *mes*, mesoderm; *s.t*, sinus terminalis; *Cho*, chorion (diplo-trophoblast).

In *Dasyurus* the allantois is vascular over a small area and comes in contact with the diplo-trophoblast (Fig. 104). But the allantoic vessels degenerate rapidly and completely, and the allantois again lies free in the cœlom. In the region of the area vasculosa the wall of the yolk-sac adheres to the uterine epithelium, and, as in the opossum, forms a simple yolk-sac placenta. The superficial capillaries of the mucosa, which are slightly dilated, are separated from the vitelline vessels by the uterine epithelium and a thin layer of fœtal ectoderm. Through the two layers the gaseous exchange probably takes place. Beyond the sinus terminalis, the non-vascular part of the wall unites over an annular zone with the uterine epithelium by enlarged ectodermal cells. These syncytial "Nährzellen" are phagocytic, and enclose fragments of epithelium and superficial capillaries. Maternal blood is effused and lies in a space between the ectoderm and entoderm, whence it is transmitted to the cavity of the yolk-sac and serves for nutriment (Hill[1]). The gestation period is about eight days, as in the opossum.

In *Perameles* the placental structures are better developed (Hill[2]). Before the attachment of the blastocyst, the uterine mucosa undergoes preliminary changes. The capillaries increase in size and new vessels are formed; the interglandular tissue is composed of a loose network of anastomosing cells and the inter-spaces are filled with lymph, the glands increase in length and diameter, and the cells of the surface epithelium lose their boundaries, and fuse to form a syncytium analogous to the *symplasma* of higher forms (see p. 445).

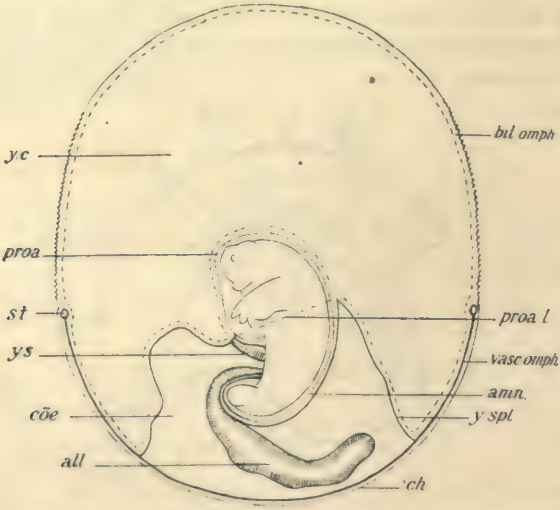

FIG. 104.—Diagram showing the arrangement of the fœtal membranes in *Dasyurus*. (From Hill, "On the Fœtal Membranes, Placentation, and Parturition of the Native Cat (*Dasyurus viverrinus*)," *Anat. Anzeig.*, vol. xviii., 1900.

amn, Trunk amnion; *all*, allantois; *bil.omph*, bilaminar omphalopleur; *ch*, chorion (diplo-trophoblast); *cōe*, extra-embryonic splanchnocele; *proa*, proamnion; *proa.l*, posterior limit of proamnion; *s.t*, sinus terminalis; *vasc.omph*, vascular omphalopleur; *y.c*, cavity of yolk-sac; *y.s*, yolk-stalk; *y.spl*, invaginated yolk-sac splanchnopleur: the ectoderm is represented by a thin line, the entoderm by a dotted line, and the mesoderm by a thick line.

Opposite the cœlom, the blastocyst becomes attached to a discoidal area of the uterine symplasma by means of enlarged ectodermal cells, and later its wall is vascularised by the allantois. Outside the disc, the part corresponding to the area vasculosa is also attached by an annular zone, and a yolk-sac placenta is formed. The non-vascular part of the wall is bathed by the uterine fluid as in the opossum (Fig. 105).

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[1] Hill, "On the Fœtal Membranes, etc., of the Native Cat (*Dasyurus viverrinus*)," *Anat. Anz.*, vol. xviii., 1900.

[2] Hill, "The Placentation of *Perameles*," *Quar. Jour. Micr. Science*, vol. xl., 1898.

In the discoid area a fuctional allantoic placenta is developed. The ectodermal giant-cells, like the early trophoblastic proliferation in man, disappear, and the allantoic vessels become firmly attached to the symplasma into which the maternal vessels penetrate. A regular interlocking of maternal and fœtal tissues is produced, and the two systems of blood-vessels are separated at the most by a thin layer of symplasma. It is not yet determined whether the yolk-sac placenta is functional till birth. According to Hill the wall probably breaks up before the end of pregnancy. The allantoic placenta, on the other hand, remains active, and at the time of birth some maternal tissue is shed, while part of the fœtal tissue is left behind. The gestation period is about eight days.

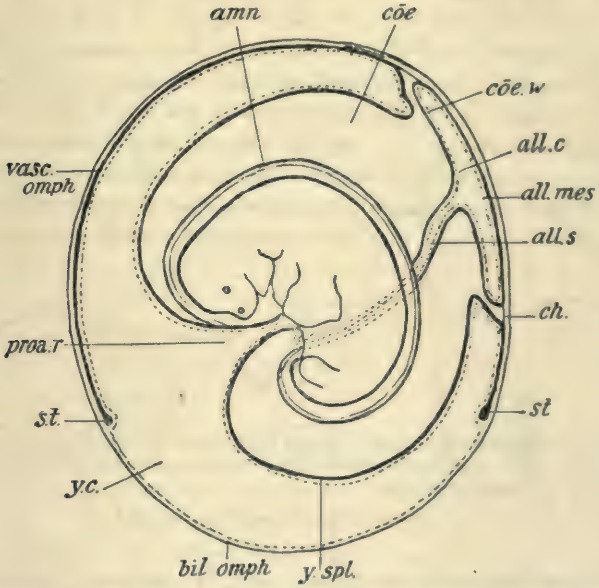

FIG. 105.—Diagram showing arrangement of fœtal membranes in *Perameles*. (From Hill, "The Placentation of *Perameles*," *Quar. Jour. Micr. Science*, vol. xl., 1897.)

amn, Amnion; *all.c*, allantoic cavity; *all.mes*, allanto-chorionic mesenchyme; *all.s*, allantoic stalk; *bil.omph*, bilaminar omphalopleur; *ch*, marginal zone of true chorion around the allanto-chorionic area; *cōe*, extra-embryonic cœlom; *cōe.w*, inner or chorionic wall of allantois; *proa.r*, persistent remnant of proamnion; *st*, sinus terminalis; *vasc.omph*, vascular omphalopleur; *y.c*, yolk-sac cavity; *y.spl*, invaginated yolk-sac splanchnopleur; ectoderm represented by thin line, mesoderm by dotted line, entoderm by thick line.

The allantois in *Perameles* is of greater importance than in the opossum or *Dasyurus*; but, relatively to the yolk-sac, it plays a small part in the nutrition of the embryo, as evidenced by the fact that the vitelline vein is thrice as large as the allantoic vein.

Ungulata.—In the sheep the blastocyst elongates early, and contains at one part the thickened embryonic area or shield (Fig. 106). From it the mesoderm reaches out on all sides. As it spreads between the epiblast and hypoblast, the cœlom is developed in it. By the thirteenth day one-third of the circumference is surrounded by cœlom, and in this area the yolk-sac is separated from the outer wall. At the seventeenth day the separation of the yolk-sac is complete all round (Bonnet[1]). It continues, however, to grow *pari passu* with the blastodermic vesicle, and is gradually pushed to one side by the enlargement of the cœlom. At the twenty-fifth day it is reduced to a solid rod of cells with a few blood-vessels on its outer surface (Fig. 107), and it disappears before the end of pregnancy (Assheton[2]). The allantois grows out into the cœlom very early and expands with extraordinary rapidity, occupying most of the cavity of the blastodermic vesicle. Its further developments are described later (p. 430). Hence in the sheep, and in the pig and cow, in which the conditions are similar, the yolk-sac is functional only from the first appearance of the vessels in the area vasculosa till about the twentieth day of pregnancy.

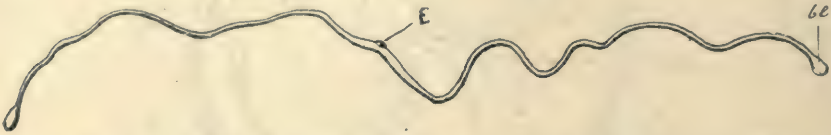

Fig. 106.—Elongated blastocyst of sheep at thirteenth day of pregnancy. (From Hertwig's *Entwicklungsgeschichte des Menschen und der Wirbelthiere*, by permission of Gustav Fischer.)

bl, Blastocyst ; *e*, embryonic shield.

In the horse there is no indication of an allantoic diverticulum at the middle of the third week, but at the end of the third week there is a considerable mass of vascularised allantoic mesoderm at the caudal end of the embryo into which a small allantoic diverticulum extends from the hind gut (Ewart[3]).

Carnivora.—The mesoblast and cœlom extend completely round the blastocyst, and the vitelline circulation is active only in the early stages. In the dog the yolk-sac is large and extends at first to the end of the citron-shaped ovum (Fig. 123). According to Bischoff[1] it persists till birth, but this is denied by Duval.[2] The allantois grows out on the dorsal side of the embryo, and fuses with the diplotrophoblast over a small discoidal area. Later, as the cavity of the allantois enlarges, it adheres to the whole of the blastocyst wall except the poles. Subsequently the zone of adhesion is reduced in extent (see p. 444).

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[1] Bonnet, "Beiträge zur Embryologie der Wiederkäuer," *Arch. f. Anat. u. Physiol.*, 1889.

[2] Assheton, "The Morphology of the Ungulate Placenta," *Phil. Trans. Roy. Soc.*, London, Ser. B., vol. cxcviii., 1906.

[3] Ewart, "Studies on the Development of the Horse : I. Development during the Third Week," *Trans. Roy. Soc. Edin.*, vol. li., 1915.

PROBOSCIDEA and HYRAX.—The elephant and the aberrant genus *Hyrax* have at full-time, like the Carnivores, a zonary placenta, but little is known regarding the development of the fœtal membranes. Assheton[3] has recently given an account of two early embryos of *Hyrax*. In the younger, the yolk-sac occupied about three-quarters of the surface of the blastocyst, and the allantois the remaining quarter, the ovum possibly being wholly embedded in the uterine mucosa. The yolk-sac was covered with a network of vessels, and the head of the embryo dipped into it. It was invested externally with a mass of trophoblastic cells, honeycombed with spaces and filled with maternal blood, but no villi were developed. In the second embryo the yolk-sac was much reduced, and was "presumably enveloped by the allantois." It had previously been shown by Turner that the yolk-sac disappeared at an early period.

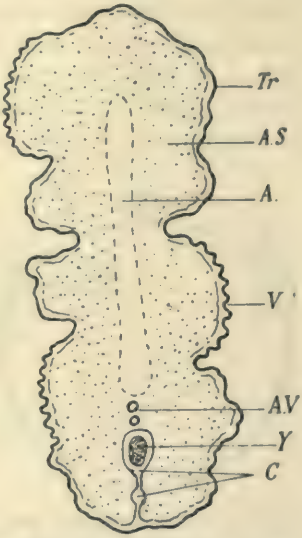

FIG. 107.—Transverse section through the blastocyst of the sheep at the twenty-fifth day. (From Assheton, "The Morphology of the Ungulate Placenta," *Phil. Trans. Roy. Soc.*, London, Ser. B., vol. cxcviii., 1906.)

A., Allantois; A.S, splanchnopleur of allantois; A.V, allantoic blood-vessel; C, cœlom; V, commencing folds from which villi spring; Y, solid yolk-sac.

RODENTIA.—In Rodents the conditions are entirely different. The mesoblast never extends, in the rabbit, rat, or mouse, completely round the ovum, and the yolk-sac hypoblast remains long in contact with the trophoblast, and carries on the nutrition of the embryo till the tardily formed allantoic placenta is developed. Regarding the partial extension of the mesoblast, Minot[1] says: "That it represents a modified condition is evident, since in all non-mammalian Vertebrates both mesoderm and cœlom extend completely round the yolk. Hence the complete separation of the yolk-sac in man and the sheep is nearer the ancestral type than the relations of the extra-embryonic germ-layers to one another in the rabbit and opossum."

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[1] Bischoff, *Entwickelungsgeschichte der Säugethiere und des Menschen*, 1842.

[2] Duval, "Le Placenta des Carnassiers," *Jour. de l'Anat. et de la Phys.*, 1893.

[3] Assheton, *Phil. Trans. Roy. Soc.*, London, *loc. cit.*

In the rabbit the mesoblast begins to spread out from the embryonic region about the end of the first week of gestation, and it gradually reaches half-way round the circumference of the blastocyst. It splits into two layers over its whole extent, and it is limited below by the sinus terminalis (Fig. 108). The lower half of the yolk-sac is non-vascular, and its wall of hypoblast is closely invested by trophoblast. Later the yolk-sac begins to shrink, taking a mushroom shape, and its vascular half comes against the non-vascular half (Fig. 109). The specially large cœlomic space, thus left by the shrinking of the vesicle, is filled with fluid through which the allantois extends to reach the part of the wall not covered by the yolk-sac. Hence at this stage the whole wall of the blastocyst is vascularised, one-half by the vitelline and the other half by the allantoic vessels.[2]

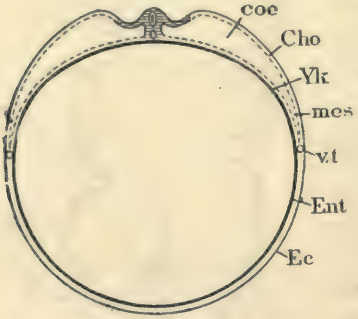

FIG. 108.—Blastodermic vesicle of the rabbit. (Minot.)

coe, Cœlom ; *Cho*, chorion (diplotrophoblast) ; *Yk*, yolk-sac ; *mes*, mesoderm ; *v.t*, vena terminalis ; *Ent*, entoderm ; *Ec*, ectoderm.

From an investigation of the early stages in the mouse and rat, Robinson[3] attaches much importance to the yolk-sac in providing for the nutrition of the embryo. On the seventh day the yolk-sac is large, and becomes invaginated with the inversion of the germinal layers (see p. 468). Outside its thin wall lies extravasated maternal blood, which is absorbed into the cavity. Over a large area the wall of the yolk-sac becomes villous with a covering of columnar hypoblast. Over a small area the trophoblast is thickened and maternal blood circulates in its spaces. But the allantois has not yet come in contact with it, and the blood "must serve only for the nutriment of the trophoblast itself." At the eleventh day the trophoblast is vascularised by the allantoic vessels, by which the nutriment is now transmitted as well as by the vitelline vessels in the yolk-villi. Then the yolk-sac becomes less important. The circulation in the decidua reflexa, which surrounds it, decreases and ceases altogether on the sixteenth day, and the wall of the yolk-sac becomes thin and bloodless. "At the same time numerous diverticula grow out from the entodermal sinus into the hilum of the allantoic placenta, and these may still absorb nutriment though they are more probably excretory." Later the outer wall of the invaginated yolk-sac undergoes atrophy and completely disappears. The remains of the yolk-sac cavity are in this way bathed in the uterine fluids. At the same time the villi of the inner wall increase in size and complexity, but whether they absorb the fluids or are entirely excretory is uncertain.

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[1] Minot, *Human Embryology*, Boston, 1892.

[2] Hertwig, *Entwicklungsgeschichte des Menschen und der Wirbelthiere*, 1906.

[3] Robinson, "The Nutritive Importance of the Yolk-Sac," *Jour. of Anat. and Phys.*, vol. xxvi., 1892.

In the spiny mouse (*Acomys caharinus*), Assheton[1] found in a well-advanced pregnancy that the yolk-sac was still extremely vascular, and covered with a columnar-celled epithelium which was much folded. The blood-vessels lay in the folds, and so approached closely to the placenta. The yolk-sac was firmly attached to the placenta over the peripheral area, but not so closely as described above for the rat and common mouse. In the spiny mouse the folds do not become involved in the placental tissues.

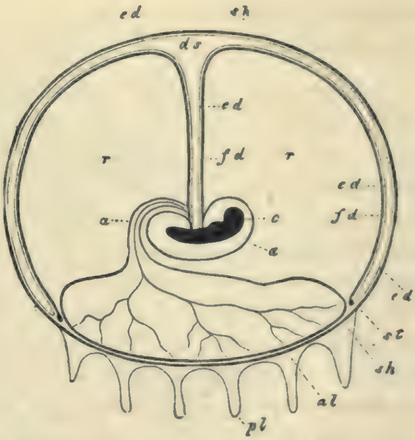

Fig. 109.—Diagram of the blastodermic vesicle of the rabbit in longitudinal section. (From Hertwig's *Entwicklungsgeschichte des Menschen und der Wirbelthiere*.)

e, Embryo; *a*, amnion; *al*, allantois with blood-vessels; *f.d*, vascular layer of mushroom-shaped yolk-sac; *d.s*, cavity of yolk-sac; *s.t*, sinus terminalis; *r*, large space filled with fluid.

The preplacental blastocyst in the beaver has been investigated by Willey[2] who states that its most conspicuous feature is the presence of a deep tract of mesoblastic origin along the length of its embryonic side. This is comparable to the "Haftstiel" of *Tarsius*, monkeys and man (see pp. 490 and 500). This structure continues to grow in later stages, and by accession of material from the uterine mucosa becomes converted into the definitive umbilico-uterine connecting membrane. In origin it is a non-vascular somatopleur or diplo-trophoblast, but in the mature fœtal sac there are intrusive capillaries proceeding into it from the vascular area. Willey suggests that the reason for the existence of the connecting membrane supplementing the placental implantation in the attachment of the fœtal sac is to be sought in the semi-aquatic habits of the beaver, which retains its activity, swimming under the ice to procure food from the submerged stock of winter provender throughout the period of gestation. Were it not for the additional support of the connecting membrane the narrow deciduous root of the massive placenta might be torn asunder.

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[1] Assheton, "On the Fœtus and Placenta of the Spiny Mouse," *Proc. Zool. Soc.*, London, 1905, vol. ii.

[2] Willey, "The Blastocyst and Placenta of the Beaver," *Quar. Jour. Micr. Science*, vol. lx., 1914.

INSECTIVORA.—In the hedgehog the yolk-sac forms a placenta which nourishes the embryo until the mesoblast splits into two layers and the allantoic placenta is formed. At a very early stage the epiblastic wall of the blastocyst has spaces in which maternal blood appears. As the mesoblast spreads out in a single layer, the area vasculosa develops, and its branches, contained in mesoblastic warts and ridges, interlock with the adjacent trophoblast to form yolk-villi (Fig. 110). The yolk-sac or *omphaloidean* placenta reaches its full development at the time when the allantois comes in contact with the trophoblast (see p. 480). Then the yolk-sac is gradually separated from the wall, more and more of its villi being peeled out from the trophoblast as the separation increases. The vitelline circulation at the same time diminishes, though it never ceases entirely (Hubrecht[1]).

In the shrew the yolk-sac adheres by a zonary strip to lateral cushions of proliferated mucosa, but the resulting yolk-sac placenta is avillous (Hubrecht[2]). The trophoblast is again thickened, and in its spaces maternal blood appears, but at a later date than in the hedgehog. The maternal blood is bodily absorbed, and at the same time the yolk-sac contains a characteristic yellowish-green, glassy coagulum with granules in it. Later the mucosal cushions disappear and the adjacent trophoblast thins (see p. 483).

In the mole a simple yolk-sac placenta persists throughout pregnancy (Robinson[3]). Unlike the hedgehog and the shrew, in which the gland lumina are plugged by the trophoblastic syncytium, there is in the mole a copious glandular secretion containing degenerated cells, which is absorbed by the trophoblast (see p. 484).

Tupaia javanica differs from the other Insectivora in having a temporary yolk-sac placenta formed in the same situation as the allantoic placenta subsequently occupies (see p. 486). The same occurs in the bat (p. 489).

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[1] Hubrecht, "The Placentation of *Erinaceus europæus*," *Quar. Jour. Micr. Science*, vol. xxx., 1889.

[2] Hubrecht, "The Placentation of the Shrew," *Quar. Jour. Micr. Science*, vol. xxxv., 1894.

[3] Robinson, Hunterian Lectures, *loc. cit.*

PRIMATES.—In monkeys, old- and new-world, there is no decidua reflexa, and a portion of the trophoblast is in contact with the uterine fluids. But even in Selenka's earliest specimens of monkeys and apes, the yolk-sac is a small, closed sac attached to the ventral surface of the embryonic area, and is entirely separated from the trophoblast. The embryonic area is connected with the inner surface of the chorion by a short stalk of mesoderm, in which the vessels run.

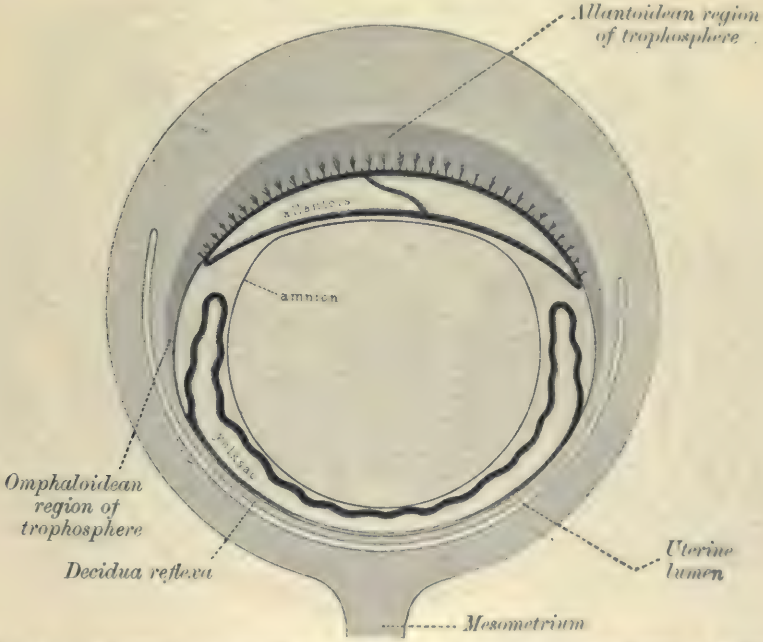
Allantoidean region of trophosphere
allantois
amnion
yolk sac
Omphaloidean region of trophosphere
Decidua reflexa
Uterine lumen
Mesometrium

FIG. 110.—Diagram to illustrate the fœtal membranes of *Erinaceus*. (From Hubrecht's "The Placentation of *Erinaceus europæus*," *Quar. Jour. Micr. Science*, vol. xxx., 1889.)

In the youngest human ovum yet examined, the yolk-sac is also a small, closed vesicle, separated from the trophoblast by a single thick layer of mesoblast (Fig. 111). The splitting of the mesoblast occurs very early, even before the appearance of the primitive streak, and the cœlom spreads round the whole circumference of the ovum. The earliest vessels appear on the under surface of the sac, and gradually extend over its upper pole, until the whole sphere is covered by a vascular network. The vessels are in direct continuity with vessels which develop in the *connecting-stalk* (see p. 490), and through them with the vessels of the chorion by a vascular loop, the *sinus ensiformis* of Eternod (Bryce[1]). This communication appears to exist before any vessels appear in the embryo itself. From the third week onwards, saccular dilatations of the entodermal lining of the yolk-sac are produced, and from their walls solid masses of cells are budded off, resembling liver-tissue in its simplest form and perhaps functioning as such (von Spee[2]). The sac grows up to the end of the fourth week. It is then pear-shaped, and is united to the intestine by a long neck in which the cavity is obliterated. The vesicle persists throughout pregnancy. Little is known of its contents; at the end of pregnancy it contains variable quantities of fatty substances and carbonates (Schultze[3]).

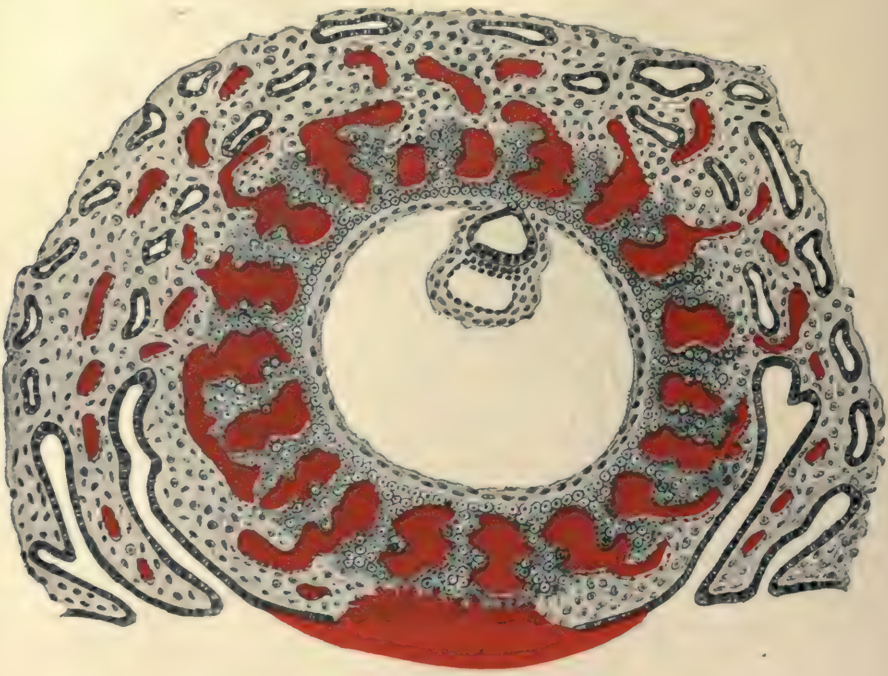

FIG. 111.—Hypothetical section of the human ovum embedded in the decidua, somewhat younger than Peters' ovum. The trophoblast is greatly thickened, and lined with mesoderm, which surrounds also the embryonic rudiment, with its yolk-sac and amnio-embryonic cavity (T. H. Bryce in *Quain's Anatomy*). The embryonic rudiment is proportionally on too large a scale.

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[1] See *Quain's Anatomy*, vol. i., Part I., 1908.

[2] *Ibid.*

[3] Schultze, "Ueber die Embryonalhüllen und die Placenta der Säugethiere und des Menschen," *Sitzungsb. d. Würzburger physik.-med. Gesell.*, 1896.

III. The Placenta in Indeciduata

In the placental Mammals an attachment takes place between maternal and fœtal tissues in the uterus, and the trophoblast is vascularised, except in the Primates, by the allantois. The method of attachment varies in different orders, and sometimes in different groups of an order. In the Indeciduata, however, the first attachment is always obtained by an *apposition* of the trophoblast to the surface of the mucosa.

Ungulata: *Pig.*—In the pig the blastocysts are spherical till the tenth day. Then they rapidly elongate, and by the fourteenth day they fill the whole length of the uterus. Subsequently they obtain a greater surface of contact by a series of concertina-like foldings (Assheton[1]), which fit between ridges of the uterine mucosa. The ridges are inter-glandular in position (Fig. 112), radiating from small circular spots, twenty or thirty to the square inch, which represent the gland-mouths (Turner[2]). It is usually stated that the uterine surface epithelium remains intact; but Assheton has recently proved that it shows signs of degeneration as early as the eighth day, and at the eighteenth day is reduced to a thin layer. Three days later, however, it again appears normal and is formed of long columnar cells, to the ends of which the trophoblast fits closely,

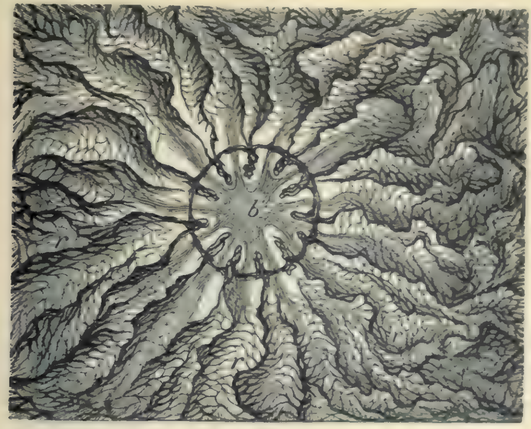

Fig. 112.—Portion of the injected chorion of the pig. The figure shows a minute circular spot (*b*), enclosed by a vascular ring, from which villous ridges (*r*, *r*) radiate (Turner). (From Balfour's *Comparative Embryology*, vol. ii. By permission of Messrs. Macmillan & Co. Ltd.)

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[1] Assheton, *Phil. Trans.*, *loc. cit.*

[2] Turner, *Lectures on the Comparative Anatomy of the Placenta*, Edinburgh, 1876.

sending protoplasmic processes between the cells (Fig. 113). These processes may even reach past the epithelium to the underlying layer of dilated capillaries (Robinson), and absorb nutritive material or effect gaseous exchanges.

The trophoblast is single-layered throughout, and, after the first three weeks, forms a syncytium. Internally to it lies the mesoblast, which in the main follows its ridges and furrows, but occasionally bridges across a fold. It is vascularised by the vessels of the allantois, which completely surrounds the embryo. The gland-mouths lie along the course of the vessels (Assheton). No formation of villi takes place, and the attachment never goes beyond the stage of apposition except for the protoplasmic extensions of the trophoblast (Fig. 114).

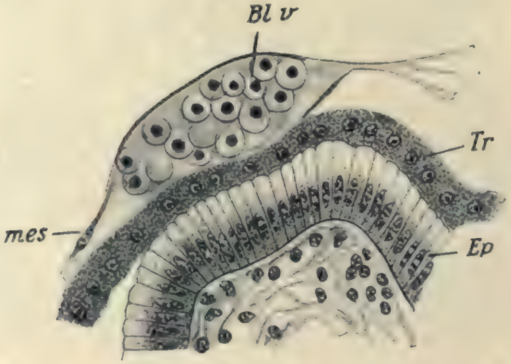

Fig. 113.—Section through the wall of the uterus and the blastocyst of the pig at the twentieth day of pregnancy (Assheton).

mes, Mesoblast ; *Bl.v*, fœtal vessel ; *Tr*, trophoblast ; *Ep*, long columnar epithelium of uterine surface.

The uterine mucosa contains no special cotyledonary areas such as are found in the sheep and cow. The surface epithelium, though it shows the degenerative changes already referred to, is apparently never completely destroyed. The glandular epithelium does not at any time show signs of degeneration. It secretes actively during the early stages, and probably during the whole of pregnancy. As in the sheep and one of the lemurs (*Galago agisymbanus*), the glandular orifices are covered by domes of trophoblastic cells, which absorb the secretion and transmit it as nutriment for the developing embryo by the allantoic vessels. The sub-epithelial tissue is gelatinous, and early in pregnancy it begins to increase in thickness by a widening of the lymphatics and blood-vessels and a new formation of capillaries. The constituents of the nutriment provided for the embryos are referred to later (see p. 432).

Mare.—In the mare the details of placental development are not yet known. In the early stages the blastodermic vesicle is attached to the uterine mucosa by the trophoblast covering the lower pole of the ovum. The trophoblast at the end of the third week differs from that of the sheep and pig and other Ungulates. Up to the sinus terminalis it consists of typical columnar cells; beyond the sinus there are (1) groups of tall columnar cells arranged to form discs which probably help to fix the blastocyst to the lining of the uterus; (2) groups of columnar cells in process of elongation; and (3) phagocytic columnar cells with sac-like processes placed around the discs and especially in shallow depressions beyond the sinus terminalis which probably lie opposite the openings of the uterine glands and are concerned in taking up the more solid particles of uterine milk (Ewart[1]).

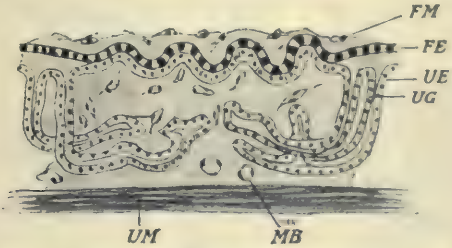

Fig. 114.—Diagram representing a stage in the formation of the placenta of the pig. (From Robinson, Hunterian Lectures, *Jour. of Anat. and Phys.*, vol. xxxviii., 1904.)

UM, Uterine muscle; MB, maternal blood-vessel; UG, uterine glands; UE, uterine epithelium; FE, fœtal ectoderm; FM, fœtal mesoderm.

Villi are formed in the allantoic region, and they fit into crypts which are probably lined with maternal epithelium. Between the fœtal and maternal tissues in the crypt is a space filled with secretion. The lymphatic system of the mucosa is enormously developed (Kolster[2]).

Sheep.—In the sheep and cow the poly-cotyledonary type of placenta is found. The former is determined by the presence from an early period, and independently of pregnancy, of numerous prominences or *cotyledonary burrs*, which project as thickened knobs of the sub-epithelial tissue into the uterine lumen. During pregnancy they form connections with localised proliferations of the trophoblast. The burrs vary in number from fifty or sixty in the sheep to five or six in the roe-deer.

The ova of the sheep reach the uterus four or five days after coitus, and the blastodermic vesicles remain free till the seventeenth day. Then the attachment to the mucosal surface begins, and it is completed by the thirtieth day (Assheton). After the ninth day, when the prochorion ruptures, the trophoblast comes in contact with the uterine epithelium. Apparently, as the result of this, the absorption of nutriment is easier, and the blastodermic vesicle increases rapidly in size so as to fill the uterine horn, or both horns if only one embryo is present.

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[1] Ewart, *Critical Period in the Development of the Horse*, London, 1897; and "Studies in the Development of the Horse," *Trans. Roy. Soc. Edin.*, vol. li., 1915.

[2] Kolster, "Die Embryotrophe placentarer Säuger, mit besonderer Berücksichtigung der Stute," *Anat. Hefte*, vol. xviii., 1902.

Certain changes occur in the mucosa before attachment. The leucocytes, which in the non-pregnant uterus are situated at the base of the lining epithelium, increase in number and penetrate between the epithelial cells. The glandular sacs, situated at the junction of the branches with the main ducts, expand greatly and actively secrete. It is generally held that the surface epithelium is not destroyed, but Assheton has shown that on the cotyledonary burrs it is distinctly degenerated by the seventeenth day, and he has also brought forward strong evidence that it is not subsequently regenerated, but is replaced by binucleate cells of the fœtal ectoderm.

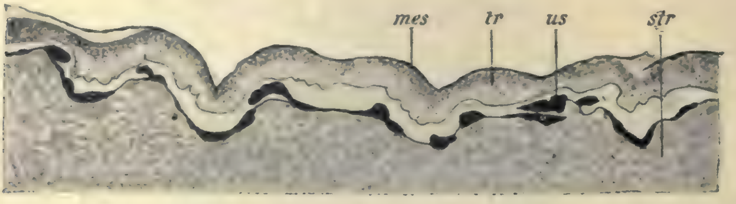

Fig. 115.—Section through the uterine and embryonic parts of a cotyledon of the sheep at the twentieth day of pregnancy. Folds in the trophoblast fitting into sulci of the cotyledonary burr. (Assheton.)

mes, Mesoblast ; *tr*, trophoblast ; *us*, degenerated uterine epithelium ; *str*, uterine stroma.

In the cotyledonary areas of the trophoblast, villi are developed as buds of epiblast, which afterwards contain cores of mesoblast with branches of the allantoic vessels (Fig. 115). They fit into depressions or crypts on the surface of the cotyledons, increase in length, and branch in different directions. Whether they literally grow into the maternal tissues either mechanically or by a phagocytic action is uncertain.[1] It seems more likely that very little, if any, further penetration occurs, but that the sub-epithelial tissue swells and keeps pace with the villi as they increase in length. The crypts, if their lining cells really belong to the fœtal ectoderm, are not secretory, and there is no free space, such as is described in the mare, between them and the villi. The sub-epithelial tissue is represented in the non-pregnant uterus by a thin layer of dense connective tissue, with localised thickenings in the burrs. With the onset of pregnancy occur an infiltration of lymph between the more superficial cells of the sub-epithelial layer, and an increase in the number and size of the blood-capillaries and lymphatics. Thus the layer becomes spongy and swells up around the fœtal villi, producing the cotyledonary interdigitation. At the fundus of the crypts the lining cells become syncytial. At the apices of the inter-crypt columns lacunæ of maternal blood are formed by repeated small hæmorrhages from the superficial capillaries (Fig. 116).

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[1] At this stage Assheton did not observe any actual engulfment of cells, but considered that nutriment might be transmitted by fine processes of the binucleate cells which united with similar processes of the connective tissue cells of the mucosa.

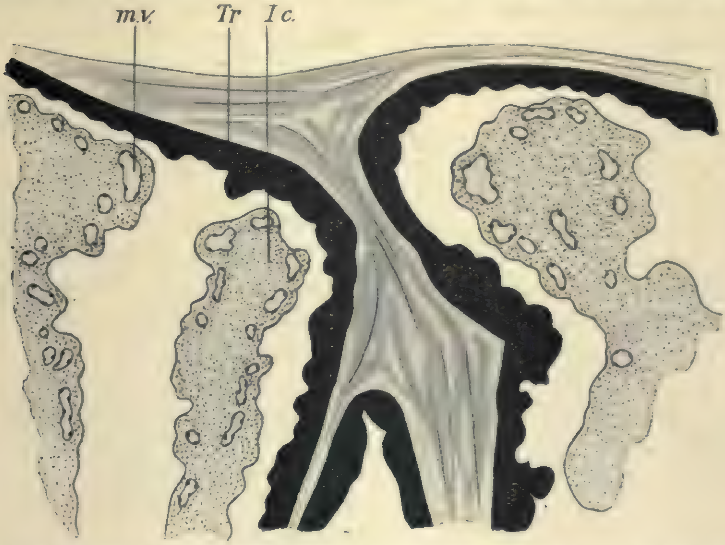

Fig. 116.—Section through the base of a fœtal villus and the apices of two inter-crypt columns. Sheep. The surfaces of the columns are traversed by large blood-vessels, which later rupture and form the blood-extravasations. (Assheton.)

Tr, Trophoblast dipping into crypt; *Ic*, inter-crypt column; *m.v*, maternal blood-vessel.

In the inter-cotyledonary area, the epithelium, whether or not it degenerates over large areas in the early stages as Assheton supposes, is later healthy and vigorous. There is no formation of a spongy layer in the sub-epithelial tissue as in the burrs. But a great change occurs in the glands, which are wholly inter-cotyledonary in position. They increase in length and complexity, and secrete actively. Towards the end of pregnancy, however, the greater part of the uterine glands is destroyed, but the surface epithelium still secretes. At the upper end of each horn the wall of the blastocyst forms a crumpled structureless membrane with no trace of nuclei, while the uterine mucosa in this region is thrown into folds and covered with a high columnar epithelium which is very active. The secretion is apparently transmitted by transfusion through the membranous wall, and is found inside the sac. At full time this part of the mucosa shows signs of great degeneration, resembling the *pulpe diffluente* of Duval in the guinea-pig (Assheton). The inter-glandular cells also hypertrophy like the connective tissue cells of Rodents.

The development and structure of the placenta of the sheep have been described at some length because the formation of the special nutriment for the fœtus has received close attention in that animal.[1]

Cow.—In the cow (Fig. 117) the placenta has essentially the same form as in the sheep, but the interlocking is not so firm. On separation of the maternal and fœtal parts of the cotyledons, the former are found to comprise the larger part. In the fully developed sheep's placenta the fœtal parts constitute the main mass of the cotyledon. The various stages of development have not been completely investigated, but one other difference has been noted, viz. the absence of lacunæ of maternal blood at the bases of the villi (Ledermann[2]).

The chorionic sac extends into both uterine cornua.

The inter-cotyledonary trophoblast is avillous in the sheep and cow. In the giraffe, however, there are rows and clusters of villi in addition to the cotyledonary villi. Simple villi between the cotyledons are also found in *Cervus*, *Oreas*, and *Tetraceros*.[3]

The Uterine Milk

The existence of a nutritive juice in the uterus of Ruminants during pregnancy has been recognised since the days of Harvey. He spoke of an albuminous fluid, which might be squeezed out from the cotyledons of the placenta, as a source of nutriment for the fœtus. As to its origin, he says in one of his Letters: "It might be transported by the uterine arteries and distilled into the uterus." The fluid was first called *uterine milk* by Needham in 1667. Haller described it as a secretion of the utricular glands, and this view was supported by Bischoff, Sharpey, and others, who considered it the immediate store of fœtal nutriment. It was analysed by Gamgee,[1] who showed that the fluid contained a large amount of protein and fat and some salts, and was thus well adapted for nutrition.

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[1] For the above account of the development and structure of the sheep's placenta, we are largely indebted to the important memoir of Assheton. Differing in many respects from previous descriptions, it alone brings forward evidence that the Ungulate placenta may be "secondarily simplified" in Hubrecht's sense (see *Quar. Jour. Micr. Science*, 1908).

[2] Ledermann, "Ueber den Bau der Cotyledonen im Uterus von Bos, etc.," *Inaug.-Dis.*, Berlin, 1903.

[3] Turner, "On the Fœtal Membrane of the Eland (*Oreas canna*)," *Jour. of Anat. and Phys.*, vol. xiv., 1879. Weldon, "Note on the Placentation of *Tetraceros quadricornis*," *Proc. Zool. Soc.*, 1884.

But Haller's view of its origin was not accepted by Turner[2] and Ercolani.[3] Turner showed that during pregnancy new crypts were formed in the cotyledons, and he supposed that the uterine milk represented the secretion of these crypts. Ercolani went even further and stated that such a secretion existed in all placentæ, but Turner was strongly opposed to this: "That such a fluid (uterine milk) is produced in all placentæ, where utricular glands or follicles continue to secrete during the whole period of placental formation, is very probable. But in the placentæ of the sloth, the apes, and the human female, where an unusual development of the maternal blood-vessels into larger sinuses takes place, a modification in the anatomical structure is produced which seems to render the presence of such a secretion unnecessary. The nutritive changes in all probability take place directly between the maternal and fœtal blood."

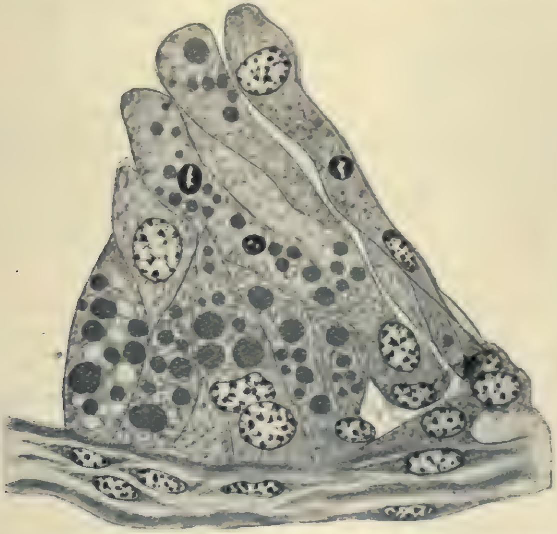

FIG. 117.—Columnar trophoblast-cells from the base of a fœtal villus of the placenta of the cow at the third month of pregnancy, to show phagocytosis. (From Jenkinson's "Notes on the Histology and Physiology of the Placenta in Ungulata," *Proc. Zool. Soc.*, London, vol. i., 1906.)

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[1] Gamgee, "On the Chemistry and Physiology of the Milky Fluid found in the Placental Cotyledons of Ruminants," *Brit. and For. Med.-Chir. Review*, 1864.

[2] Turner, "The Placentation of the Sloths," *Jour. of Anat. and Phys.*, vol. viii., 1874.

[3] Ercolani, "Sull' unita del tipo anatomico della placenta," *Mem. dell' Accad. di Bologna*, 1876.

More recent investigations have thrown fresh light on the origin, composition, and absorption of uterine milk. It must be recognised that, even before the onset of pregnancy, changes occur in the uterus which are important for the nourishment of an embryo developing later. Shortly before the first œstrous period, the mucosa "matures" by the formation of the richly cellular sub-epithelial layer of connective tissue already referred to (see p. 431). Among Indeciduates it is specially well marked in the cotyledonary types. With the first proœstrum the mucous membrane becomes œdematous, and the superficial capillaries are dilated. Many of them rupture and give rise to miliary hæmorrhages, which later undergo changes such as occur in hæmorrhages elsewhere. Whether the changes are caused by an enzyme action on the part of the leucocytes is uncertain; but in any case the white corpuscles take up the pigmented products of disintegration, and then arrange themselves in a row, or in groups, close under the surface epithelium in the manner described in an earlier chapter (Chapter III., p. 105). Some of the leucocytes contain unaltered hæmoglobin, as is shown by the characteristic reaction with eosin; others contain derivatives of it, in which iron may often be demonstrated. With the onset of pregnancy these cells wander out between the epithelial cells, and mingle with the secretion lying in the uterine cavity. This secretion is poured out by the superficial and glandular epithelium, which becomes more active at the beginning of pregnancy with the increased flow of blood and lymph through the mucosa. It forms the more fluid part of the uterine milk in which the formed constituents lie. It is necessarily found only in the *extra-cotyledonary* regions since no glands exist in the burrs.

Besides the intracellular pigments, there is another source of iron, though in widely varying amounts. In all placental Mammals a greater or less amount of maternal blood is in direct contact with the trophoblast. In the pig and mare it is restricted to individual red blood corpuscles, which find their way to the surface and mingle with the gland secretion. In the ass Strahl[1] has found blood in greater amount, forming small effusions. In the sheep its presence has often been noted by Tafani,[2] Bonnet,[3] and others. The position of the extravasations in the placenta has been already referred to (see p. 431). In the cow they are apparently not a constant phenomenon, the supply being often restricted, as in the mare, to a few single erythrocytes. In the deer, blood is effused into the glands, but no extravasations take place in the cotyledons. Here the whole of the maternal part of the burr appears to be digested and absorbed by the trophoblast. The greater activity of the fœtal ectoderm in the deer is also shown by the destruction of the epithelium over the whole surface of the uterus (Strahl[1]).

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[1] Strahl, see Hertwig's *Handb. d. vergl. u. exp. Entwickelungsg. d. Wirbelthiere*, 1902.

[2] Tafani, "Sulle Condizioni utero-placentari della Vita Fetale," *Arch. della Scuola d'Anat.-Path.*, Firenze, 1886.

[3] Bonnet, "Ueber Embryotrophe," *Deut. med. Woch.*, 1899.

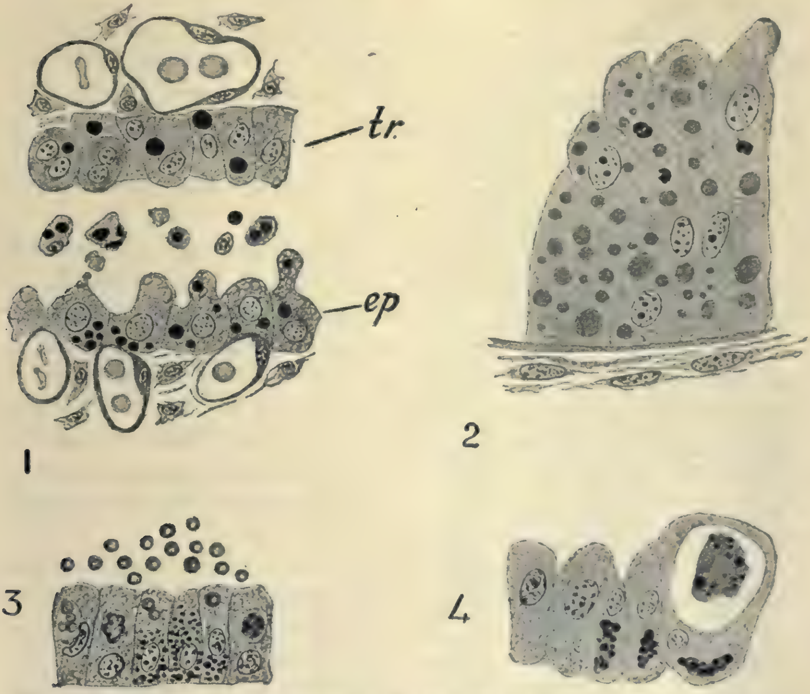

Fig. 118.—Histology of the placenta in the cow and sheep. (From Jenkinson, *Vertebrate Embryology*, Oxford, at the Clarendon Press.)

1. Fœtal and maternal tissues in a cotyledon. *tr*, Trophoblast of a villus; the cells are absorbing fat (black). In the trophoblast are binucleate cells. Behind it are the connective tissue and blood-vessels of the allantois. *ep*, Uterine epithelium lining a crypt. Fat secretion is going on, the ends of the cells with fat globules being pinched off and thrown into the crypt's lumen. Below the epithelium are maternal capillaries and connective tissue.
2. Columnar trophoblast cells form between the bases of the cotyledonary villi. The cells contain ingested matter (corpuscles, nuclear, and cell débris).
3. Ingestion of extravasated maternal corpuscles by the trophoblast in the sheep. The cells contain pigment besides corpuscles.
4. Deposition of pigment derived from hæmoglobin of ingested corpuscles in trophoblast cells of cow. The pigment granules (black) are deposited in irregular masses.

In addition to blood, the uterine milk contains fat in large quantities. Before pregnancy it may be demonstrated in the subepithelial leucocytes which later migrate to the surface. Fat globules are also contained in large amount in the epithelial cells of the surface and glands. According to Bonnet, it cannot be considered as a fatty degeneration because the cells are otherwise healthy; it is rather a fatty infiltration, the epithelium secreting it from the lymph or blood-plasma, storing it and later giving it off to the uterine milk.

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[1] Strahl, "Ueber die Semiplacenta multiplex von *Cervus elaphus*," *Anat. Hefte*, H. xciii., 1906.

Kolster[1] has described a process by means of which cellular elements are added to the "Embryotrophe."[2] The gland epithelium proliferates so strongly that the cells cannot find room in the wall, and tracts of them are invaginated into the lumen. Later the cellular projections, sometimes along with some of the underlying connective tissue as in the mare, are cut off and added to the embryotrophe (Fig. 119).

Traces of glycogen may be extracted from both the maternal and fœtal parts of the cotyledons, but it is too small in amount to be demonstrated histologically. It is also present in small amounts in the extra-cotyledonary areas—in the uterine epithelium both superficial and glandular in the cow, in the sub-epithelial connective tissue in the sheep, and in the uterine milk (Jenkinson[3]). Large quantities of glycogen are stored in the *plaques amniotiques*, localised masses of cells on the internal surface of the amnion, and later on the umbilical cord. In the calf embryo the *plaques* reach their full development about the sixth month, and then gradually atrophy.

It is obvious that the uterine milk must contain many elements which have not been mentioned individually. The product of conception requires numerous other substances for its development besides protein, fat, carbohydrate, and iron. Organic phosphorus compounds are furnished by the nuclei of cells, and these may also contain iron. In general the fixation of mineral elements is slight at the beginning of pregnancy, but becomes active towards the end. But the requirements vary at different periods of pregnancy. For example, sodium decreases and calcium increases with the replacement of cartilage by bone, and potassium increases with the increased manufacture of red blood corpuscles. These and many other substances are present in uterine milk though not demonstrated histologically. Either they have been dissolved by the fixative, or have remained unstained by the methods hitherto employed.

One other constituent has been described by various observers, but its composition and significance are unknown. Besides the leucocytes that contain pigment granules and fat, others are filled with rod-like bodies, the "Uterinstäbchen" of Bonnet.[1] Later they appear in the uterine milk. Rods have also been described in the trophoblast of the rabbit by Beneden, and in the uterine mucosa by Schmidt,[2] who stated that they were composed of calcium oxalate. In Ruminants they are found in enormous numbers, but whether they form a supply of calcium for the fœtus is not known (Fig. 121). There is at present no evidence that they are "protein crystals," a name sometimes applied to them.[3]

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[1] Kolster, "Die Embryotrophe placentarer Säuger, etc.," *Anat. Hefte*, vols. xviii. and xix., 1902 and 1903.

[2] Objections have been raised to the term "uterine milk" because the fluid contains cellular elements, pigment granules, etc., which are not present in the mammary secretion. Bonnet and his followers have employed the convenient term "Embryotrophe," but it must be noted that in the sheep it forms the nutriment long after the *embryonic* stage of the developing ovum is past. The two terms are used indiscriminately in this chapter.

[3] Jenkinson, "Notes on the Histology and Physiology of the Placenta in Ungulata." *Proc. Zool. Soc.*, London, 1906, vol. i.

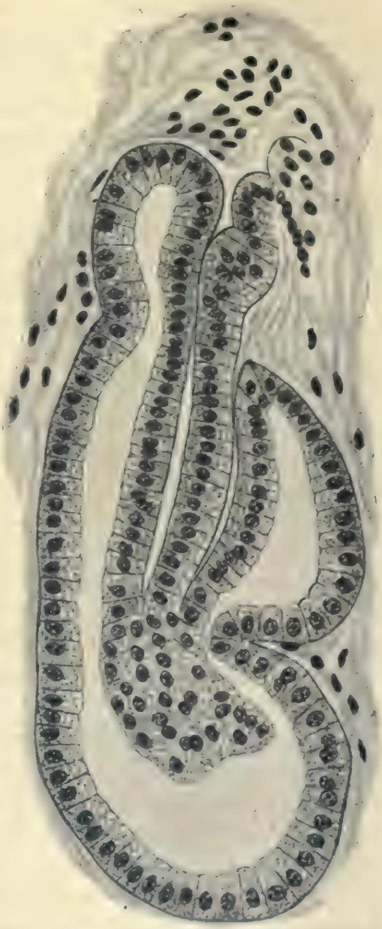

FIG. 119.—First stage of cellular secretion in the placenta of the cow. Invagination of glandular epithelium and some of the underlying connective tissue. (From Kolster, "Die Embryotrophe placentarer Säuger," *Anat. Hefte*, vols. xviii. and xix., 1902-03.)

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[1] Bonnet, "Beiträge zur Embryologie der Wiederkäuer gewonnen am Schafe," *Arch. f. Anat. u. Phys.*, Anat. Abth., 1884.

[2] Quoted by Bonnet, "Ueber Embryotrophe," *Munch. med. Woch.*, 1899.

[3] Jenkinson (*Vertebrate Embryology*, London, 1913) has described "the curious, rounded or elongated, often flattened, bodies, sometimes soft, sometimes hard and brittle, found floating in the allantoic fluid, and familiar for many centuries under the title of 'hippomanes.' In the cow they are white or pale yellow, in the sheep a dirty brown. In the sheep they are formed by local accumulations of the viscid uterine milk, which get into pockets of the trophoblast between the cotyledons. Gradually, pushing the trophoblast and allantois in front of them, they make their way into the cavity of the latter, in which they lie attached by a stalk to the wall; the stalk narrows and breaks, and they are free in the cavity. At first they are surrounded by a membrane—the remains of their covering of allantois and trophoblast—and are soft; they are composed of granular coagulable material, full of cell-detritus, degenerating nuclei, globules of fat and glycogen, and leucocytes. Later the membrane disappears, and the bodies become hard by being saturated with calcium oxalate in the form of 'envelope' crystals. In the cow, when outside the chorion and still soft, they are a bright orange colour, due to the presence of bilirubin, doubtless derived from the extravasated corpuscles eaten by the trophoblast;

The uterine milk has thus the following constituents—the secretion of the superficial and glandular epithelium, perhaps mingled with lymph transuded from the œdematous mucosa; leucocytes containing hæmoglobin derivatives, fat globules, and "Stäbchen"; glycogen; tracts of glandular epithelium set free by a process of "cellular secretion"; red blood corpuscles and their derivatives; connective tissue elements; salts, etc., which are in solution and not recognisable by ordinary histological methods.

While lying free in the uterine cavity, the uterine milk undergoes changes which consist largely in a disintegration of its cellular elements. The leucocytes degenerate and their cytoplasm, with the pigment granules, fat globules, and "Stäbchen," is set free. The tracts of glandular epithelium are also transformed into a mass of débris, and their contents lie free in the embryotrophe. The red blood corpuscles may be ingested almost unaltered by the trophoblast, or they may first be laked, and the hæmoglobin may be absorbed as such, or undergo changes before absorption. According to Jenkinson, hæmoglobin is broken up into an iron-containing and iron-free part. The former is carried away by the fœtal blood-vessels and stored in large quantities, principally in the fœtal liver, as a reserve for use during lactation. The iron-free part is deposited in the cells as a pigment, occurring in such amount as to give, especially in the later stages of pregnancy, a deep brown colour to the fœtal cotyledons. It collects at the apices of the villi, and its presence suggests that the cotyledons are actively engaged in excretion (Assheton). The histological changes in the red blood corpuscles absorbed by the trophoblast have been described by Jenkinson. They are engulfed by amœboid processes of the cells, and gradually become paler in colour and irregular in outline; often they clump together. Gradually yellowish-brown granules are deposited on the surface of the included cells, and this process continues till the whole is converted into a dark brown mass. Bonnet called the granules hæmatoidin crystals, but Jenkinson was unable to demonstrate this pigment in alcoholic extracts of the placenta. He found two other pigments, one absorbing a small part of the violet end of the spectrum, and the other showing two absorption bands, which differed slightly from those of oxyhæmoglobin in neutral solution and of hæmatoporphyrin in acid solution. This pigment is obviously a hæmoglobin derivative, and from it bilirubin may be formed. It is present in the sheep and cow during pregnancy, but not in the virgin uterus of the sheep. A similar yellowish-brown pigment

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they are, indeed, found at the bases of the villi, just where these extravasations occur. Large allantoic bodies impregnated with calcium oxalate are found in the horse" (see Fig. 101 above).

occurs in the crypts and the tissues outside them, and also, according to Assheton, in the maternal blood-stream. It is not yet possible to explain the exact significance of these changes. The iron-free pigment is apparently a waste product, and the iron-containing part is stored in the fœtal organs. Whether the fœtus subsequently synthesises part of the organic iron compound into hæmoglobin, or absorbs minute quantities of hæmoglobin as such, according to its requirements, is unknown.

The cotyledonary and inter-cotyledonary parts of the placenta present differences both anatomically and physiologically. In the inter-cotyledonary region are the glands, and here only are found the gland-secretion and the "cellular" secretion. In the cotyledonary parts the glands are absent. Here the villi are formed, and they effect an attachment to the mucosa by the greater activity of the trophoblast. Assheton has suggested that this hyper-activity may be stimulated by the absence of glands and consequently of uterine milk in the cotyledons, the fœtal ectoderm attacking the mucous membrane more vigorously in order to obtain food. The blood effusions are also cotyledonary, and the eosin and iron reactions are obtainable in the adjacent trophoblast, and not at other places. Finally, it is probable that the exchange of oxygen and carbonic dioxide is carried out in the cotyledons. Here the maternal capillaries are more dilated than outside the burrs, and they come close up to the surface, some of them even impinging on the lining membrane of the crypts. Between them and the allantoic vessels in the villi intervene only a small amount of mesoblast, the cellular trophoblast, and the lining of the crypts which, according to Assheton, corresponds to the plasmodiblast of the bat. In the inter-cotyledonary regions, on the other hand, the fœtal vessels are related to the orifices of the glands, and appear to be concerned principally with the absorption of their secretion. As already mentioned, the villi may also be concerned with the excretion of waste products of hæmoglobin.

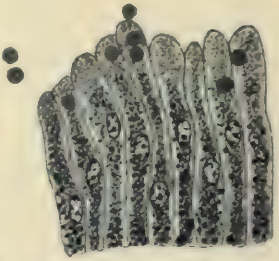

Fig. 120.—Ingestion and disintegration of red blood corpuscles by the trophoblast of the sheep. (From Jenkinson's "Notes on the Histology and Physiology of the Placenta in Ungulata," *Proc. Zool. Soc.*, London, vol. i., 1906.)

Bonnet was the first to show that the trophoblast in Ruminants was actively phagocytic and absorbed the constituents of the uterine milk (Fig. 120). He demonstrated the presence of fat globules, hæmoglobin and its derivatives, degenerated leucocytes and "Stäbchen" (Fig. 121)—in short, all the histologically demonstrable constituents of the embryotrophe—in the trophoblast. Many, if not all, of the cellular elements are partially degenerated before absorption. The appearances suggest an enzyme action on the part of the trophoblast, and perhaps also the leucocytes, but no proteolytic or lipolytic enzyme is contained in glycerin extracts of the maternal or fœtal part of the cotyledon.

After their absorption, the disintegration of the cellular constituents is completed in the trophoblast, and they are no longer recognisable as individual elements. Their products are transmitted to the fœtal vessels, though they may first be elaborated in the trophoblast into a form or forms suitable for the use of the embryo in the development of its various organs.

LEMUROIDEA.—Many of the lemurs have a simple avillous diffuse placenta, as Turner[1] first pointed out in specimens from Madagascar. Hubrecht has investigated two others found in the East Indies—*Tarsius*[2] and *Nycticebus*.[3] The latter has also a diffuse placenta. Villi develop over the whole of the chorion, and fit into vascular crypts in the uterine mucosa from which they are easily retracted at birth. The epithelium of the crypts persists as in the cow, and the "osmotic interchange takes place through two cell-layers of different origin, and of different physiological significance (phylogenetically). *Tarsius* approaches more closely to the Insectivora and Primates. The trophoblast proliferates and penetrates into the mucosa, and maternal blood circulates in its spaces. The mesoblast grows profusely, and forms with the trophoblast a true chorion in Hubrecht's restricted sense. The placenta is discoid. In *Galago agisymbanus*, Strahl[4] has shown that a layer of secretion lies between the uterus and the ovum from the beginning of pregnancy. It is absorbed by the ectoderm, the cells of which are vesiculated over the gland orifices. Many blood extravasations occur in the connective tissue of the mucosa, and the red blood corpuscles undergo changes as in the sheep, the glandular cells and embryotrophe containing granules which give an iron reaction. At the extremity of each chorionic villus is a slight pit the cells surrounding which contain a granular greenish substance derived presumably from hæmoglobin. Turner[5] had previously noted in lemurs the intense brown staining of the glands from effused blood.

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[1] Turner, "On the Placentation of the Lemurs," *Phil. Trans. Roy. Soc.*, London, vol. clxvi., 1876.

[2] Hubrecht, "Ueber die Entwicklung des Placenta von Tarsius, etc.," *Internat. Congr. of Zool.*, Cambridge, 1898.

[3] Hubrecht, "Spolia Nemoris," *Quar. Jour. Micr. Science*, vol. xxxvi., 1895.

[4] Strahl, "Die Verarbeitung von Blutextravasaten durch Uterindrüsen," *Anat. Anzeig.*, vol. xvi., 1899.

[5] Turner, "The Placentation of Lemurs," *Jour. of Anat. and Phys.*, vol. xii., 1878.

Jenkinson[1] has lately investigated the placenta in a species of *Lepilemur* and found that it conforms in structure to those of other members of the Lemuroidea excepting Tarsius. "In the Lemuroid placenta the relation between fœtal and maternal circulations is brought about by the production of vascular trophoblastic villi, which fit into crypts lined by a persistent uterine epithelium. So the placenta, therefore, resembles that of an ungulate: it is of the so-called 'Indeciduate' type. The allantois is large and occupies a great

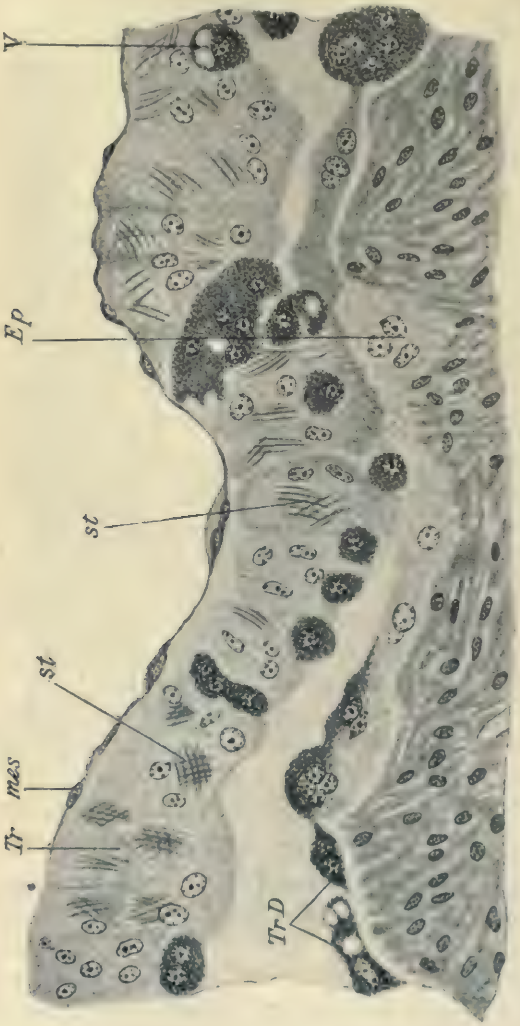

Fig. 121.—Absorption of "Stäbchen" by the trophoblast of the sheep. (Assheton.)

mes, Mesoblast; *Tr*, trophoblast containing "Stäbchen" (*st*); *Tr.D*, binucleate trophoblast cells; *Ep*, uterine epithelium undergoing absorption by the trophoblast; *V*, vacuolated cell.

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[1] Jenkinson, "The Placenta of the Lemur," *Quar. Jour. Micr. Science*, vol. lxi., 1915.

deal, if not the whole, of the space between the amnion and the chorion."

CETACEA.—There is a diffuse indeciduate placenta in *Orca*, uniformly studded with branched villi which are absent only at the ends of the chorionic sac, that is, opposite the os uteri and the Fallopian tubes. The sac extends into both cornua.

SIRENIA.—The placenta in *Halicore* is diffuse, indeciduate, and zonary (see above, p. 408). The uterine epithelium persists in the crypts. "Stäbchen" or hippomanes (see p. 437) have been found.

EDENTATA.—The placenta is said to be zonary and deciduate in *Orycteropus* (unlike most Edentates), bell-shaped in *Myrmecophaga* and *Tamandua*, poly-cotyledonary in *Bradypus*, oval in *Dasypus*, and diffuse in *Manis* and *Cholœpus*.[1] The details of placental development have not been worked out in any of these animals and the constitution of the embryotrophe is unknown.

IV. THE PLACENTA IN DECIDUATA

In the Deciduata three modes of attachment between embryo and mother are found: *Centric*, in which the blastocyst rests in the cavity of the uterus, attains a large size, and comes in contact with the wall over its whole circumference; *Excentric*, in which the blastocyst remains small and lodges in a furrow of the uterine mucosa, and later a decidua reflexa is formed; *Interstitial*, in which the small blastocyst attacks the mucosa at one point and reaches the connective tissue. In this form also a decidua reflexa is formed.

In the neighbourhood of the attachment the mucosa degenerates, but the connective tissue cells usually enlarge to form decidual cells before degeneration sets in.[2] The capillaries dilate and come in contact with the trophoblast. The mucosa interlocks so closely with the fœtal villi that the two tissues cannot be separated without injury.

CARNIVORA.—The Carnivora are characterised by a zonary form of deciduate placenta. The following account of its development refers particularly to the dog and cat, which have been most frequently investigated. The gestation period in the cat is on an average sixty days, and in the dog fifty-eight to sixty-three days. In both the ovum takes a comparatively long time to traverse the oviduct. On reaching the uterus the blastocyst is covered by a thick prochorion which prevents adhesion for a considerable period.

The mucosa is matured, as in Ungulates, at the first prœstrum by the development of a well-differentiated sub-epithelial cellular layer, and of the glands and crypts (see p. 430). The crypts provide an increase of superficies and of secreting epithelium, and are later concerned in the attachment of the ovum. They have been recognised by all the authorities with the exception of Robinson,[1] who states that he can find no evidence that any of the crypts are other than the ducts of the uterine glands. At the first and each succeeding procestrum there is a marked hyperæmia of the mucosa, and from the rupture of

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[1] Jenkinson, *Vertebrate Embryology*, Oxford, 1913.

[2] But see p. 457.

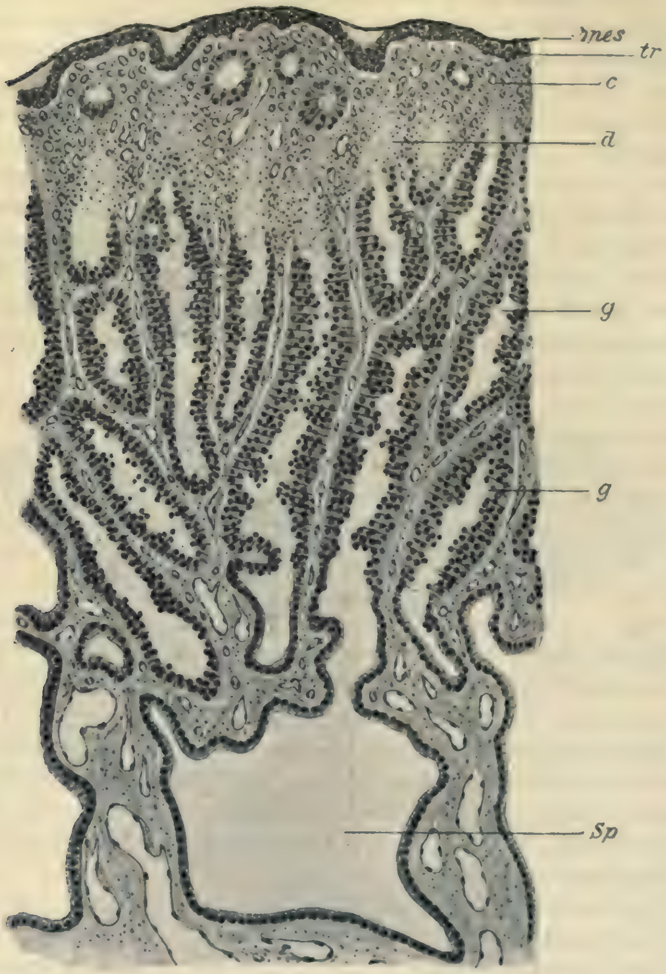

FIG. 122.—The uterine mucosa of the dog about the twenty-third day of pregnancy. (From Duval's "Le Placenta des Carnassiers," *Jour. de l'Anat. et de la Phys.*, 1893.)

mes, Mesoblast; *tr*, trophoblast; *c*, capillary layer; *d*, layer of glandular detritus; *g*, glands of compact layer; *Sp*, dilated glands of spongy layer.

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[1] Robinson, Hunterian Lectures, *Jour. of Anat. and Phys.*, vol. xxxviii., 1904.

some of the superficial capillaries miliary hæmorrhages occur (see Chapter III.).

At the beginning of pregnancy, blood effusions are found close under the surface of the mucous membrane, but bleeding into the uterine cavity, which took place during the prœstrum, has entirely ceased. The epithelium of the surface glands and crypts is swollen and pervaded with minute fat globules in the dog (Bonnet[1]) and cat (Melissenos[2]). The glands widen quickly into "chambers," and tracts of their proliferated epithelium are invaginated, and often obliterate the lumen. The widening of the glands and crypts makes the deep layer *spongy*. The capillaries increase and form practically the whole of the sub-epithelial layer. Immediately below it lies the layer of glandular ducts which are obliterated by débris resulting from the degeneration of the proliferated epithelial cells. Between it and the spongy layer is the compact layer, also formed from the sub-epithelial layer. In it the glands are not so widely dilated and the connective tissue is more abundant (Fig. 122).

The embryotrophe at this stage differs from that in Ungulates. The glandular secretion is less fluid, perhaps because the lymph transudate is less abundant (Kolster[3]). It surrounds the ovum to form the prochorion or "Gallertschicht," and is, according to Bonnet,[4] absorbed by the trophoblast.

When the prochorion disappears, the fœtal ectoderm already has proliferated over a broad zone of the citron-shaped ovum (Fig. 123), to form villosities which attack the surface of the mucosa, and obtain an attachment to it—about the twentieth day in the dog (Duval[5]) and the twelfth day in the cat (Robinson). Vascular processes of the allantois grow into the centre of the trophoblastic villi, first over a limited discoid area, and later over the whole zone as the allantois spreads round the wall. Hence the rudimentary placenta is discoid and the completed placenta zonary.

In procuring attachment to the uterus many of the villi project into glands and crypts. According to Strahl,[6] the epithelium lining the ducts and the surface of the uterine cavity is then transformed into a syncytium and invests the villi externally. Heinricius[7] is of opinion that the epithelium disappears, and the syncytium is formed by the uterine connective tissue. But it is now generally recognised that the syncytium is trophoblastic. It has been proved by Strahl himself, and by Duval, that many of the villi obtain attachment at parts of the surface where there are no gland openings or crypts, and penetrate into the substance of the mucosa. Before the disappearance of the epithelium, the cells lose their outlines and form a homogeneous mass of protoplasm with fragmented nuclei. This degenerated tissue ought not, as Bonnet[1] emphasised, to be known as *syncytium*, which represents an active protoplasmic condition (see p. 398). The name which he suggested, *symplasma*, is very convenient and is used here. It is not only the surface epithelium which forms a symplasma. The glandular epithelium, the connective tissue cells, and extravasated blood may also give rise to a symplasma which may be designated *glandular*, *connective tissue*, and *hæmatogenous* respectively. All are formed to a large extent in the placenta of Carnivores, and their resemblance to the trophoblastic syncytium has led to much confusion.

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[1] Bonnet, "Beiträge zur Embryologie des Hundes," *Anat. Hefte*, vol. xx., 1902.

[2] Melissenos, "Ueber die Fettkörnchen und ihre Bedeutung in der Placenta bei den Nagern und der Katze," *Arch. f. mikr. Anat.*, vol. lxvii., 1906.

[3] Kolster, "Ueber die Zusammensetzung der Embryotrophe der Wirbelthiere," *Ergebn. d. Anat.*, vol. xvi., 1906.

[4] Bonnet, "Ueber das 'Prochorion' des Hundekeimblase," *Anat. Anzeig.*, vol. xiii., 1897.

[5] Duval, "Le Placenta des Carnassiers," *Jour. de l'Anat. et de la Phys.*, 1893.

[6] Strahl, "Die histologischen Veränderungen d. Uterusepithel. in d. Raubthierplacenta," *Arch. f. Anat. u. Phys.*, Supplement, 1890.

[7] Heinricius, "Ueber die Entwicklung und Struktur der Placenta beim Hunde," *Arch. f. mikr. Anat.*, vol. xxxiii., 1889.

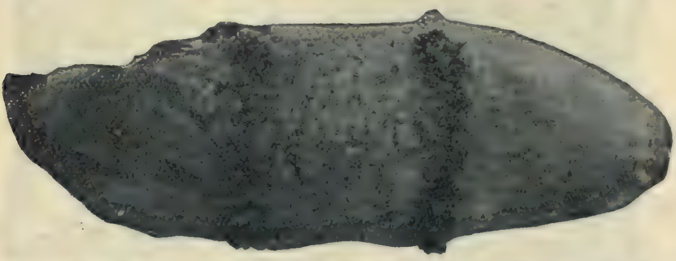

Fig. 123.—Ovum with zonary band of villi. (From Hertwig's *Entwicklungsgeschichte des Menschen und der Wirbelthiere*, by permission of Gustav Fischer.)

After the destruction of the epithelium, the villi penetrate into the deeper tissues of the mucosa by gradually absorbing the symplasmata, and branch to form secondary and tertiary villi. When the ectoderm reaches the capillary layer, it sends out protoplasmic processes which encircle the dilated vessels. The trophoblast on the sides of the villi becomes syncytial, but retains its cellular character at the tips. Internally the villi contain vascular cores of mesoblast. Hence is formed the *angioplasmode* of Duval—a continuous layer of fœtal vascular villi, clad with syncytium, penetrating everywhere into the capillary layer, and leading to a disappearance of all the maternal tissues except the vessels (Fig. 124). By the epithelial arcades at the tips, the layer of villi rests on the sheet of glandular detritus and the compact layer, which in turn form a symplasma and undergo absorption. Thus the fœtal structures reach the spongy layer, in which the glandular *culs-de-sac* have expanded to form large cavities separated by partitions, the mesenteriform lamellæ. Gradually the roof of this layer is also absorbed by the trophoblast, and the ectodermal arcades at the tips of the villi gain a permanent attachment to the mesenteriform lamellæ. At the same time, by the further branching and penetration of the fœtal mesoderm in the *angioplasmode*, the tissue is broken up into a series of labyrinthine lamellæ, which consist of a network of maternal vessels clothed on each side by syncytial trophoblast. The meshes of the

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[1] Bonnet, "Ueber Syncytien, Plasmodien und Symplasma, etc.," *Monatsschr. f. Geburtsh. u. Gynäk.*, vol. xviii., 1903.

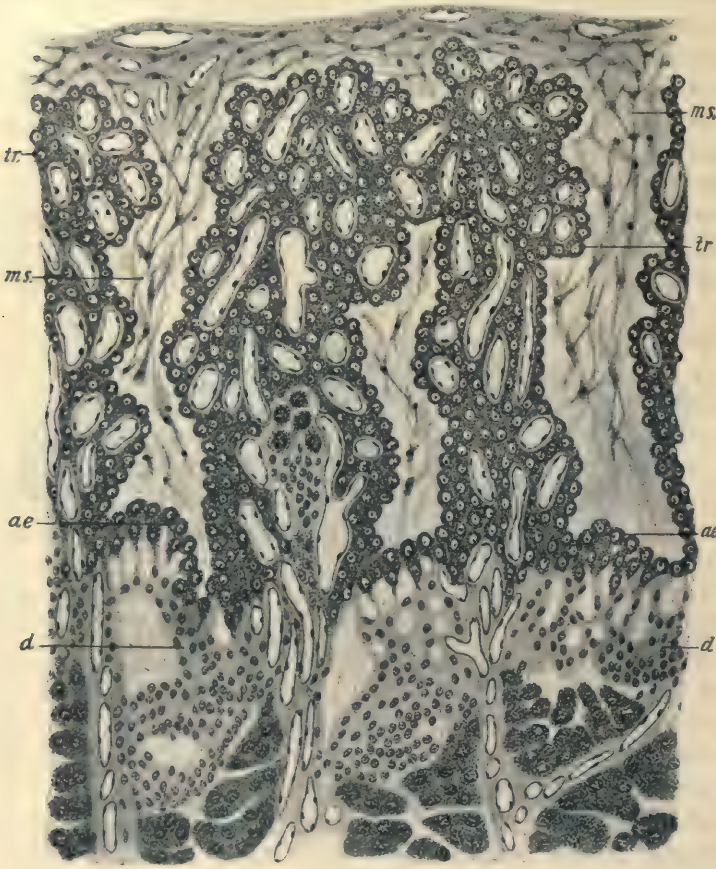

FIG. 124.—The angioplasmode of the dog at the thirtieth day of pregnancy. (From Duval's "Le Placenta des Carnassiers," *Journ. de l'Anat. et de la Phys.*, 1893.)

ms, Mesoblast ; *tr*, trophoblast ; *ae*, ectodermic arcades ; *d*, layer of glandular detritus.

network are penetrated by the vessels of the villi. In this way, according to Duval, the *labyrinth* is formed. In it the maternal and the fœtal blood are separated by the endothelium of the uterine capillaries, a cellular layer (considered fœtal by Duval and maternal by Heinricius) which later disappears, the syncytium, mesoblast, and fœtal capillary walls.

At places, however, the villi come directly in contact with maternal blood, especially at the "green border" of the placenta, which forms a characteristic appearance in some of the Carnivora. In all the members of the order, larger or smaller maternal hæmorrhages occur at an early period after the attachment of the blastodermic vesicle. The effusions vary in size and position. In the dog they occur regularly along the margins of the placental zone, and form the *bordure verte*; in addition smaller hæmorrhages take place into the substance of the placenta, and form the "green pockets," which may be isolated or joined to the green border by bridges (Fig. 125). In the cat the hæmorrhages occur in irregular positions and do not assume the green colour typical of the dog. Indications of a green border are present in the earlier stages, but

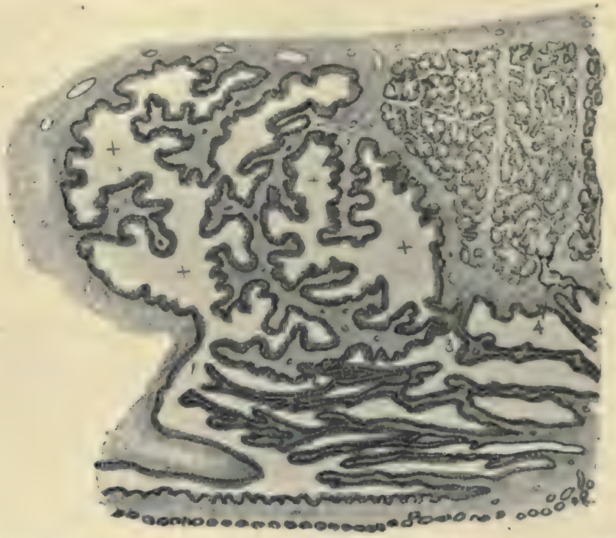

FIG. 125.—The labyrinth and the green border of the placenta of the dog at the fortieth day of pregnancy. To the right are two lobules of the angioplasmode which have reached the stage of complexity of the labyrinthine lamellæ: to the left is the green border, the cavities of which, normally filled with blood, are indicated by a cross. (From Duval's "Le Placenta des Carnassiers," *Jour. de l'Anat. et de la Phys.*, 1893.)

1, 2, and 3, Basal lamellæ of the green border; 4, basal lamella of lobule of labyrinth.

not in the completed placenta. In the otter and badger the effusion takes the form of a large blood-pouch, filled with a great variety of blood derivatives. In the ferret the conditions are similar; the main effusion occurs at the anti-mesometrial border of the uterus, and divides the zone into two lateral discs. According to Robinson, it lifts the trophoblast from the decidua, and forces it in the form of irregular pouches towards the interior of the ovum. Strahl and Bonnet also state that the blood is effused between the mucosa and the blastodermic vesicle, and thus is contained in spaces whose walls are maternal on the one side and fœtal on the other. According to Duval the blood-spaces are entirely lined by trophoblast, and with the advance of the villi other and larger hæmorrhages occur, coalescing to form the green border and islands. In either case the trophoblast is in direct contact with maternal blood. There the wall of the blastodermic vesicle is avillous but strongly folded, the ends of the ectodermal cells are expanded like clubs, and their protoplasm becomes coarsely reticular. Into the meshes the constituents of the green pulpy mass, unaltered erythrocytes and hæmoglobin or its derivatives, are absorbed by phagocytosis.

From the preceding account, it is clear that certain resemblances and certain differences exist between Carnivora and Ungulata in the composition of the embryotrophe. The most notable difference in the zonary placenta is the absence of the large amount of milky fluid which arises in the sheep from the glandular secretion and the transudation of lymph. In Carnivora the gland secretion is less important. Though the deep parts of the glands which lie in the glandular layer may secrete, the epithelium of the more superficial parts proliferates, and then degenerates and loses its secretory function; finally it forms a symplasma which plugs up the lumen of the glands.

On the other hand, the amount of nutriment furnished directly from the maternal blood is increased. It is found in the extravasations already described, and as individual blood corpuscles and droplets of hæmoglobin or its derivatives in the lumina of glands. Leucocytes are found during the whole of pregnancy, but in less abundance than in the sheep. They do not act to the same extent as store-houses of fat, but some of them, the *siderophores*, contain granules which give an iron reaction. In the course of pregnancy they disappear comparatively early, with the exception of a few in the deep glandular layer. Fat is found in the intact epithelium of the glands, and in the lumen after desquamation of the cells. It appears in the epithelium partly as an infiltration and partly as a degeneration product of the protoplasm.

In the Carnivora the fœtal ectoderm of the zonular band of attachment attacks the uterine mucosa more strongly than in the Ungulata. As a result, the maternal tissues, with the exception of the septa containing the placental vessels, disappear down to the middle of the spongy layer, and the tissue which is destroyed serves as pabulum for the developing embryo. Van der Brock[1] suggests that the general œdema of the uterine mucosa may lead, as elsewhere, to its malnutrition and degeneration, and thus it may fall an easy prey to the trophoblast. Others maintain that the degeneration is brought about by a trophoblastic influence, perhaps of the nature of an enzyme action. The result is a transformation of all the elements to a symplasma. In the cat the connective tissue cells may form large decidual cells before their final destruction.

As in the Indeciduates, there is strong histological evidence that the trophoblast is actively phagocytic, and takes up, as it meets them, the constituents of the prochorion, and later the degenerated tissues and extravasated blood. In the neighbourhood of the extravasations active absorption is indicated by the change in shape of the trophoblast cells and by their pigmentation. In the mesoblast of the villi and its vessels no trace is found of any of the formed elements of the embryotrophe, a proof that they undergo further transformation in the trophoblast after absorption.

The interchange of oxygen and carbonic dioxide apparently occurs in the labyrinth, as in the cotyledons of the sheep. Here only is the fœtal circulation brought into close proximity with circulating maternal blood. Other fœtal waste products are probably also got rid of in the labyrinth. Nolf[2] suggests that the excretory products may be responsible for the degeneration of the maternal tissues into a symplasma.

In how far the other substances necessary for the growth of the embryo are taken up respectively from the circulating blood by purely physical or physiologically selective processes, and from the extravasated blood effusions by direct phagocytosis, is not known.[3]

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[1] Van der Brock, "Die Eihüllen und die Placenta von *Phoca vitulina*," *Petrus Camper*, D. ii. Quoted by Kolster (*Ergebn. d. Anat.*, vol. xvi., 1906).

[2] Nolf, "Étude des modifications de la muqueuse utérine pendant la gestation chez le murin," *Arch. de Biol.*, vol. xiv., 1896.

[3] Cunningham has investigated the fluid and salt interchanges between mother and fœtus in cats in the later stages of pregnancy. He injected into the venous system balanced solutions of potassium ferrocyanide and iron ammonium citrate, salts which can be precipitated as Prussian blue, and consequently can be readily followed along the route traversed to their ultimate location. It was found that both maternal and fœtal endothelia were easily permeable to the two salts, but fœtal ectoderm reacted differently in terms both of permeability and length of time required. In experiments of short duration no trace of either salt was found in the amniotic fluid, fœtal urine, or tissue extract. In those of longer duration sodium ferrocyanide was found in the amniotic fluid and fœtal urine, but no trace of iron ammonium citrate was ever detected in any fœtal tissues. The placenta in the shorter experiments showed

It has been shown that the fœtal fat in the dog is not necessarily derived directly from fat fed to the mother, for Thiemich[1] fed a dog on widely different fats (palmitin and linseed oil, etc.) during two successive pregnancies but found the fat in the fœtus to be the same in each case (see below, p. 543).

PROBOSCIDEA.—In the elephant, the allantois is large and vesicular. Short villi are developed over a large area of the blastodermic vesicle. They lodge in pre-existing depressions in the uterine wall, but the trophoblast is inactive and does not attack the maternal tissues (Assheton[2]). Over a zonary area, however, the villi are much longer, and, penetrating deeply into the maternal tissues, they form a large mass of tissue in the meshes of which maternal blood *circulates.* Hence the zonary placenta differs from that of Carnivores and resembles that of Insectivores, in which, however, the maternal blood circulates in trophoblastic spaces before the advent of fœtal capillaries.

Though no red blood corpuscles appear to be absorbed as such by the trophoblast, there is evidence of an active absorption of hæmoglobin derivatives, the presence of iron compounds being easily demonstrated, especially in the cores of the villi and the walls of the fœtal capillaries. In the syncytial trophoblast, however, the Prussian-blue test is negative (see p. 511).

At birth the long villi are left *in situ* and absorbed by the maternal tissues.

HYRAX.—As in the elephant, the placenta of *Hyrax* has been studied only in isolated specimens, and its development is not known. According to Assheton,[3] the trophoblast is probably thickened all round the wall of the blastocyst, as in the hedgehog and man, but there is no appearance of a decidua reflexa. Maternal blood is carried directly to the fœtal side of the trophoblast, where it is close to the fœtal vessels, and so may provide nutriment. It then trickles back through a complicated system of lacunæ in the trophoblast.

The placenta is at first diffuse and later zonary. In the mucosa

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Prussian blue in the maternal endothelium, but none within the ectoderm. In the longer experiments blue granules had penetrated the ectodermal layer, but not the fœtal endothelium. The placental ectoderm thus shows a marked selective behaviour. (Cunningham, R. G., "Studies in Placental Permeability—I. The Differential Resistance to Certain Solutions Offered by the Placenta in the Cat," *Amer. Jour. of Physiol.*, vol. liii., 1920.) See also below, p. 466, footnote.

[1] Thiemich, "Über die Herkunft des Fötalen Fettes," *Zent. f. Phys.*, vol. xii., 1898.

[2] Assheton, "The Morphology of the Ungulate Placenta, with Remarks on the Elephant and *Hyrax*," *Phil. Trans. Roy. Soc.*, London, Ser. B., vol. cxcviii., 1906.

[3] Assheton, *loc. cit.*

of the placental area the glands disappear early, and a great increase in the interglandular stroma occurs, as in Rodents.[1]

Rodentia.—Among the Rodents there are variations in the mode of attachment. It is centric in the rabbit, excentric in the mouse and rat, and interstitial in the guinea-pig. In all the ultimate form of the placenta is discoid.

It was in Rodents that the proliferation and vascularisation of the trophoblast were first described by Selenka.[2] Later Duval[3] gave a fuller account of the earlier stages, and Hubrecht discovered the same conditions in other orders.

Rabbit.—The fertilised ovum of the rabbit, clothed by the prochorion, reaches the uterus at the beginning of the fourth day after coitus. At first it has no fixed position; but by the seventh day, when the blastocyst is about five millimetres in diameter, the prochorion lies so closely on the surface of the uterus that it fixes the ovum. At the end of the eighth day the prochorion ruptures, and the blastodermic vesicle probably collapses at the same time by injury to its wall.[4]

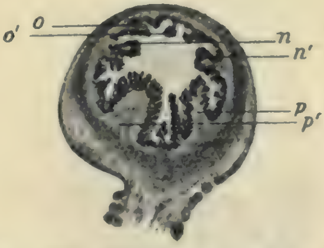

Fig. 126.—Transverse section of a four days' gestation sac of the rabbit. The mucosa is differentiated into six definite folds. The two folds nearest the mesometrium are the largest and mark the site of placental attachment. (From Chipman's "The Placenta of the Rabbit," *Labor. Rep., Roy. Coll. Phys.*, Edinburgh, vol. viii., 1903.)

p, p′, Placental folds; *n, n′*, peri-placental folds; *o, o′*, ob-placental folds.

The "mature" uterine mucous membrane of the non-pregnant rabbit already shows specialised structures, which are of importance for the attachment and nutrition of a future embryo. These consist of symmetrical pairs of longitudinal folds, first described by Hollard,[5] and subsequently named by Minot:[6] *placental* folds, the largest, situated one on each side of the groove corresponding to the insertion of the mesometrium; *ob-placental* folds, the smallest, opposite the mesometrium; *peri-placental* folds, intermediate in position and size (Fig. 126). Each fold is divided by transverse fissures into rectangular areas, the *coussinets* of Hollard. At the onset of pregnancy two of these areas on the placental folds, placed one on either side of the mesometrial groove, hypertrophy and form the maternal part of the future discoid placenta (Bischoff[1]), which is thus bi-lobed (Fig. 127). The folds of the mucosa are essentially increased areas of the mucosal connective tissue, but they differ from the cotyledons of Ruminants in having glands.

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[1] Hubrecht (*Quar. Jour. Micr. Science*, 1908) draws attention to the peculiar position of *Hyrax*. It has many archaic peculiarities, and has been placed near Rodents, elephants, and Ungulates by different authors. Yet its placental characters resemble those of the hedgehog and man. This he takes as strong evidence that the type of placenta found in *Hyrax*, the hedgehog, and man diverges less widely from the primitive type than the placenta of Ungulates and Rodents.

[2] Selenka, *Keimblätter und Primitivorgane der Maus*, 1883.

[3] Duval, "Le Placenta des Rongeurs," *Jour. de l'Anat. et de la Phys.*, 1889-92.

[4] See Hertwig's *Entwicklungsgeschichte des Menschen und der Wirbelthiere*, 1906.

[5] Hollard, "Recherche sur le Placenta des Rongeurs," *Annales des Sciences Naturelles*, 1863.

[6] Minot, "Die Placenta des Kaninchens," *Biol. Centralbl.*, vol. x., 1890.

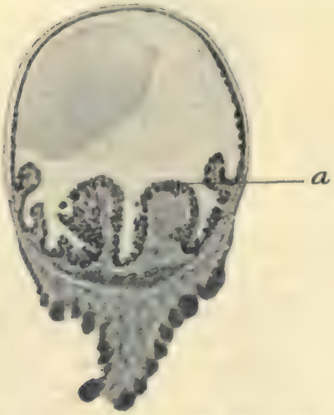

FIG 127.—Transverse section of a seven days' gestation sac of the rabbit (Chipman). The placental folds (*coussinets*) are large (*a*): the muscular walls of the sac are thin.

On the entrance of a fertilised ovum into the uterus, the folds, especially the ob-placental, become shortened, and a localised actual cavity appears which is occupied by the blastocyst. At the same time there is a marked hyperplasia of the cellular connective tissue of the placental and peri-placental folds, leading to a thickening of their bases (Chipman[2]). By the sixth day the capillaries are also increased in these regions. In the ob-placental folds appear enormous giant-cells, derived by a process of "degenerative hypertrophy" from the epithelium of the surface and glands.[3] They persist till at least mid-pregnancy, and are probably absorbed by the trophoblast overlying the yolk-sac. In the placental lobes the epithelial cells proliferate and fill up the superficial *culs-de-sac* of the mucous membrane. The glands are as yet unchanged, and the increased blood supply leads to a free secretion which is usually considered to be added to the albumen-layer, and then to be absorbed by the trophoblast. There is no appreciable transudation of lymph such as occurs in Ruminants.

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[1] Bischoff, *Entwickelung des Kaninchen-Eies*, Braunschweig, 1842.

[2] Chipman, "Observations on the Placenta of the Rabbit, with Special Reference to the Presence of Glycogen, Fat, and Iron," *Lab. Rep., Roy. Coll. Phys.*, Edinburgh, vol. viii., 1903. The development of the placenta is carefully traced in a complete age-series of pregnant rabbits and admirably figured by many photo-micrographs. The account as given here is based mainly on Chipman's monograph, but the phraseology is sometimes changed.

[3] Mr Hammond suggests that these may be detached cells from the trophoblast. *Cf.* Hammond, "On the Causes Responsible for the Developmental Progress of the Mammary Glands in the Rabbit," *Proc. Roy. Soc.*, B., vol. lxxxix., 1917.

As the blastodermic vesicle grows, it presses against the folds and levels them. Hence at the time of attachment the surfaces of the placental lobes are nearly regular. The covering epithelium again returns to normal, but the active proliferation of the connective tissue cells is continued to form the placental cotyledons. At the same time the trophoblast proliferates in concentric areas on either side of the embryonic rudiment, which is placed opposite the groove between the placental cushions. Here the ovum is generally said to gain its first attachment, the ob-placental lobes having by this time disappeared.[1]

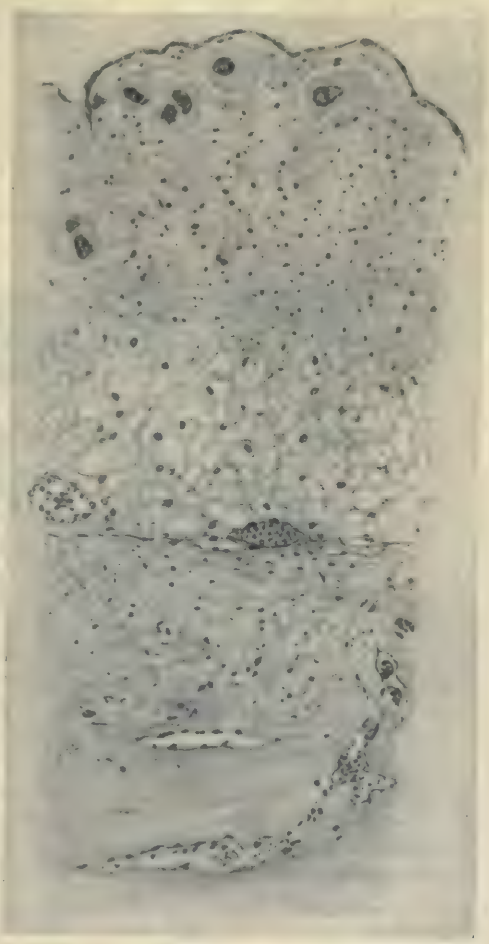

FIG. 128.—Section through uterine mucosa of rabbit pregnant about eighteen days. The section shows decidual tissue and, near the surface, giant-cells which are supposed to be detached trophoblast cells, and therefore of fœtal origin. (From Hammond.)

Where the maternal and fœtal tissues are in contact, the surface epithelium shows a form of degeneration similar to the epithelial symplasma of the zonary placenta—fusion of cells and fragmentation of nuclei. It is attacked by the thickened, horse-shoe-shaped trophoblast, the *ectoplacenta* of Duval, and its edge presents microscopically a "bitten or corroded appearance." This phagocytic or chemical action leads later to the complete disappearance of the epithelium, so that the trophoblast comes in contact with the connective tissue of the uterus. The glands are dilated, and their proliferated endothelium forms a symplasma which blocks the lumina. At these places the trophoblast advances more quickly, as if the resistance was weaker, and the line of attachment is undulating (Fig. 129). The dips thus correspond to the gland orifices and represent the beginnings of the future villi. The blood-vessels are large and numerous and have no adventitia, *i.e.* they are wholly capillaries. But the more deeply placed of them acquire an adventitia, the *perivascular sheath* (Masquelin and Swaen[1]). It is formed of one or two layers of large connective tissue cells which represent the first appearance of the decidual cells. After the destruction of the superficial and glandular epithelium, the trophoblast advances into the interglandular tissue, the cells of which degenerate in turn and are absorbed. The advance is most rapid where a capillary is met with.

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[1] Assheton (*Quar. Jour. Micr. Science*, vol. xxxvii., 1895) states that the trophoblast shows papillary thickenings over the ob-placental and peri-placental lobes, and that by them the ovum obtains the first attachment over its lower pole.

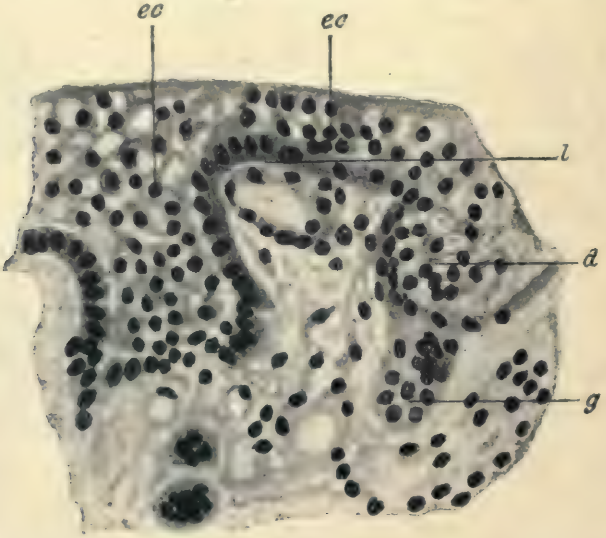

FIG. 129.—Thickened ectoderm (ectoplacenta) in the rabbit, attached to placental lobe and dipping more deeply at the position of the glands. (Chipman.)

ec, Fœtal ectoderm ; *l*, line of attachment of ectoderm ; *d*, fœtal ectoderm dipping into placental gland ; *g*, terminal *cul-de-sac* of placental gland.

The mucous membrane is now differentiated into two zones, the *intermediary region* and the *region of the uterine sinuses* (Duval). The intermediary region lies superficially. It is closely packed with fusiform stroma cells and capillaries with thin perivascular sheaths of *uninucleate* decidual cells. "It suggests a reaction of the maternal placenta to the 'parasitic' fœtal placenta" (Chipman; see also p. 403). By the influence of the trophoblast the decidual cells increase in size and become *multinucleate* (Maximow[1]). They lose their perivascular position and pervade the whole of the region. In their formation all traces of the gland ducts are lost, the cells of the latter appearing to serve as pabulum for the decidual cells. In the *region of the uterine sinuses* the blood-vessels dilate to form large spaces, and the decidual cells remain uninucleate till a considerably later period. The junction between the two zones is marked by the blind ends of the glands, which are filled with degenerated epithelium. In section each appears as an island of glandular symplasma.

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[1] Masquelin and Swaen, "Développement du placenta maternel chez le lapin," *Bull. de l'Acad. Roy. de Belg.*, 1879.

At the tenth day the allantois joins the outer wall of the blastocyst over the site of the future placenta. The trophoblast of this region is differentiated into two layers, the plasmodiblast and the underlying cytoblast. The latter disappears before the end of pregnancy. Processes of vascular mesoblast invade the trophoblast at intervals, and break it up into columns. At the same time the fœtal tissues continue to advance and surround maternal capillaries, the endothelium of which they replace. In the zonary placenta of Carnivora the trophoblast surrounds the vessels without destroying the endothelium. In the rabbit the ectodermal processes are hollow tubes which surround the vessels; they are closed on the fœtal side and open on the maternal side. Their cavity is filled with maternal blood, and externally lies the cytoblast and vascular mesoblast. Such are the "villi." Subsequently the arrangement becomes more complex, each hollow column being divided up into a series of hollow tubes parallel to the original column, and each tube in turn forming a series of hollow tubules. At each division the thickness of fœtal tissue between the maternal blood in the axis and the fœtal vessels decreases, till finally there is only a film of trophoblast and the vascular wall. At places the trophoblast even is wanting, and the fœtal endothelium alone intervenes between the two blood-streams.

The endothelium of the maternal capillaries frequently ruptures just before it is overtaken by the ectoderm, and irregular blood extravasations are formed, and later surrounded by trophoblast. In the deeper layers of the intermediary region, according to Chipman, capillary hæmorrhages occur more slowly, and give rise to a fibrinous tissue with red and white blood corpuscles scattered through it. This is similar to the hæmatogenous symplasma of Bonnet. It gradually increases in amount, and extends to the region of the uterine sinuses.

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[1] Maximow, "Zur Kenntnis des feineren Baues der Kaninchen-Placenta," *Arch. f. mikr. Anat.*, vol. li., 1897. See also *ibid.*, vol. lvi., 1900.

While the fœtal ectoderm advances along the vessels, it remains stationary at the non-vascular parts. Hence there is an interlocking of maternal and fœtal tissues, and peninsulæ of multinucleate cells come to lie between the projections of the trophoblast. At the same time the intermediary region decreases in thickness, and the ectoderm reaches the superficial sinuses of the deeper zone. Here the uninucleate decidual cells again become multinucleate, apparently at the expense of the blood symplasma, in the same manner as formerly at the expense of the glandular symplasma. The sinuses enlarge, and their walls proliferate into several layers of degenerated cells, which after mid-term are gradually replaced by laminæ of fibrin.

At a later period the intermediary zone still further decreases in thickness, and the multinucleate cells gradually "melt to form a granular detritus" (Duval). At the end of pregnancy the maternal placenta consists almost entirely of blood and blood symplasma, except for a thin rim of tissue containing blood-sinuses at the zone of separation. The gestation period is thirty days.

As compared with the placenta of Carnivora, it is obvious that the dilatation of maternal vessels is much more marked in the rabbit, and throughout the placenta the maternal blood is in direct contact with the trophoblast, and not only at the border or round a blood-pouch. The blood is not degenerated to a sufficient extent to exhibit the varieties of pigmentation found in the zonary placenta. Chipman does not state whether the maternal blood circulates in the trophoblastic tubes, but Maximow[1] says that it does. Similarly Duval says: "The maternal blood *circulates* from the fœtal extremity towards the maternal extremity of a lobule" (*i.e.* the series of tubules derived from one tube). According to Masius,[2] "the maternal blood *circulates* in an ectodermal mass of fœtal origin." Herein lies a great difference between the placentæ of Rodents and Carnivores or Ungulates. In the sheep the main nutriment is furnished by the glands; the maternal blood which is in contact with fœtal ectoderm is stationary and small in amount, and serves chiefly as a supply of iron; the exchange of gases takes place through fœtal and maternal tissues. In the dog the gland secretion is less important; the blood is again stationary and restricted to certain situations, and it shows markedly degenerative appearances, but it is greater in amount, and probably furnishes other substances besides iron for the fœtus; in the *angioplasmode* the maternal blood circulates and here the exchange of gases is effected, but again both maternal and fœtal tissues intervene between the two blood-systems. In the rabbit the glandular secretion is still less important after attachment, and even the blind ends do not secrete; throughout the placenta there is normal *circulating* maternal blood in direct contact with fœtal tissues, and it serves both as nutriment and for the exchange of gases. In addition, there are stationary blood extravasations which are engulfed by the trophoblast, but they are subsidiary. Both in the dog and the rabbit there is a marked formation of symplasma which may be connected, as Bonnet suggested for the dog and Maximow for the rabbit, with the slowing of the circulation in the placenta, or may be the result of a trophoblastic influence.

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[1] Maximow, "Die ersten Entwicklungsstadien der Kaninchenplacenta," *Arch. f. mikr. Anat.*, vol. lvi., 1900.

[2] Masius, "De la Genèse du Placenta chez le Lapin," *Arch. de Biol.*, 1889.

In the placenta of the rabbit there is one other difference which marks it off from the placenta of Carnivores and links it with Insectivores and man—the connective tissue cells of the mucosa form decidual cells. They assist to an important degree in the preparation of nutriment for the embryo. They exercise a phagocytic action on the neighbouring degenerated maternal tissues, glandular remnants and fibrin, and so attain their greatest development, while at the same time they become store-houses of fœtal nutriment. At a later period they degenerate and are absorbed by the trophoblast. Their possible function as a protection against the attack of the fœtal ectoderm has already been mentioned. At the end of pregnancy their defence is no longer required, as the trophoblast has also lost its activity. The so-called "decidual cells" of the Carnivora are a later and different formation.

Iron Metabolism

The decidual cells are concerned in the metabolism of iron, fat, and glycogen for the fœtus. In the rabbit, as contrasted with Ruminants, the ingestion of healthy or degenerated erythrocytes probably does not occur. Though Maximow states that they are "present in the plasmodium," they appear to be *in* the plasmodium only as the isolated peninsulæ of decidual cells are in it, *i.e.* they lie in spaces surrounded by trophoblast. Whether hæmoglobin as such or its more immediate derivatives in the form of *organic* iron compounds are absorbed has not been investigated, but Chipman has shown that *inorganic* iron compounds are present, and their distribution speaks for their absorption by the trophoblast. The compounds appear as blue-black granules in sections stained with a weak watery solution of hæmatoxylin. At the fourteenth day they are present in the fœtal mesoblast, especially where it approaches the decidua. They increase in size and number for a few days and then diminish, but some are still seen at the end of pregnancy. A few granules appear in the trophoblast between the sixteenth and twentieth days (Fig. 130). From the sixteenth day they are also found in an increasing number of the decidual cells which lie close to the fœtal placenta; after the twenty-fourth day, when the cells degenerate, the granules are no longer discrete, but there are irregular blue-black patches up to the end of pregnancy.

Such isolated data cannot be accurately interpreted. The fact that the deposits in the three tissues are always situated in apposition to each other speaks for their absorption by the fœtal tissues; on the other hand, a very small number of granules are present in the trophoblast, and only for a few days. It is possible that *organic* iron compounds, not shown by the hæmatoxylin stain, are absorbed and broken up, and later appear as granules in the mesoderm. Their further course to the fœtal liver, in which they are stored, has not been traced. It is to be noted that the iron compounds are not only derived from hæmoglobin. They may also represent degeneration products of the nucleoproteins.

Hubrecht[1] has suggested that erythrocytes may be manufactured in the decidual cells, and their iron-containing granules may thus be utilised (see p. 518).

Fat Metabolism

Regarding the presence of fat in the placenta of a rabbit, a few observations have been made by Eden,[2] Maximow, and Masius. Chipman has investigated the subject in greater detail, but he draws no conclusions from the histological data. In reality, the study of fat in the placenta is rendered difficult by its occurrence both as an infiltration and in the degeneration of cells.

Fat is found in the fœtal viscera, liver, heart, and mid-gut, before the allantoic circulation is established. At this time, the tenth day, the vitelline circulation is at its height, and the fat probably reaches the embryo by its vessels, as it is also found in the hypoblast of the area vasculosa. It may be derived from the absorption by the trophoblast of fat droplets contained in the giant-cells of the peri-placental folds. As the vitelline circulation diminishes, the fat disappears from the embryonic viscera, and does not reappear till four or five days after the establishment of the allantoic circulation. During this interval fat is present in the extra-placental wall of the blastocyst, but it probably arises by a degeneration of its cellular protoplasm.

In the fœtal placenta, fat is never found in the mesoblast or capillary walls, but it occurs in the trophoblast, especially where it is in contact with maternal blood or decidua. It increases from the twelfth to the sixteenth day, then it decreases, and a week later disappears altogether. In the maternal placenta fat first appears in the decidual cells which are nearest the trophoblast. They show no sign of degeneration at this time, and they probably *secrete* the fat globules. After increasing for a few days, it diminishes with the atrophy of the decidual cells, and finally appears as fatty débris. Fat is also present in the proliferating endothelium, and later in the fibrin laminæ of the uterine sinuses.

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[1] Hubrecht, "Ueber die Entwicklung der Placenta von Tarsius und Tupaja," *Internat. Congr. of Zool.*, Cambridge, 1898.

[2] Eden, "The Occurrence of Nutritive Fat in the Human Placenta," *Proc. Roy. Soc. London*, vol. lx., 1896.

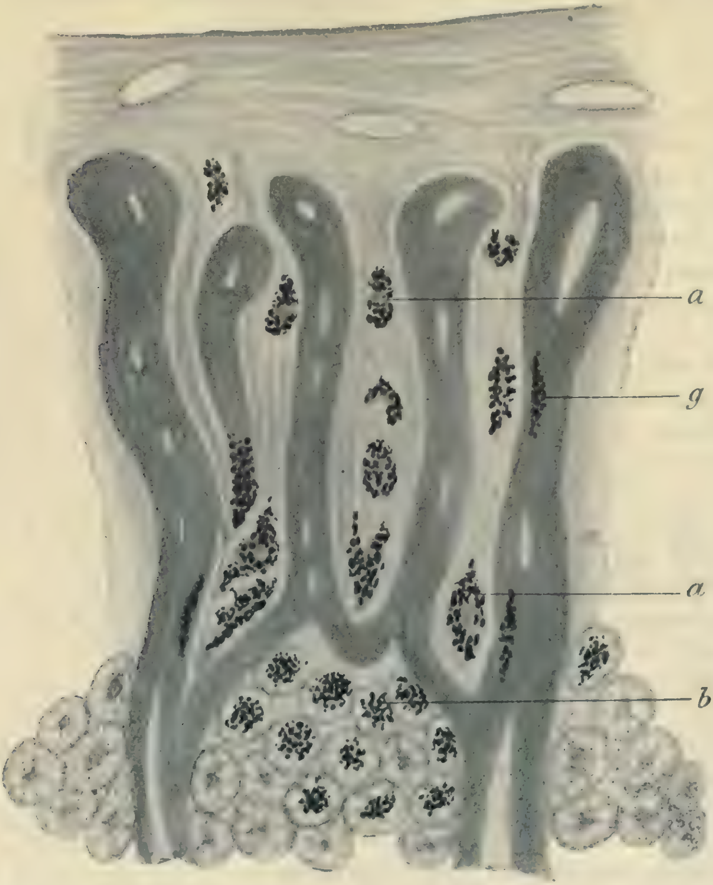

Fig. 130.—Iron granules in the placenta of the rabbit at the eighteenth day of pregnancy. (Chipman.)

a, Iron granules in mesoblast; *b*, iron granules in multinucleate decidual cells; *g*, iron granules in ectodermal tubules.

In the new-born fœtus the main store of fat is contained in the subcutaneous tissue. It is remarkable that it does not appear in this situation till the greater part of the fat has disappeared from the placenta. It is either transmitted to the fœtus in a form which does not reduce osmic acid, or formed in the fœtus itself from other substances. At birth the fœtal viscera, especially the liver, have a considerable store of fat which increases during suckling.

Glycogen Metabolism

The presence of glycogen in the placenta of the rabbit was discovered by Claude Bernard[1] in 1859. He showed its increase and subsequent decrease during pregnancy, and concluded from his observations that the placenta carried out for the fœtus, in the first half of intra-uterine life, the glycogenic function subsequently assumed by the fœtal liver. Godet[2] described two areas of glycogen-containing cells, one immediately underlying the fœtal villi, the other in the deeper part of the placenta. Maximow investigated these cells at different stages of pregnancy; he found glycogen in the decidual cells of the vascular sheaths at the eighth day, gradually increasing in amount and playing an important part in the nourishment of the trophoblast. In the later stages glycogen disappeared and the decidual tissue was transformed into polygonal multinucleate cells rich in fat. Chipman recorded detailed observations in a more complete age-series from the eighth day to the end of gestation. He showed that glycogen was always present in the maternal part of the placenta, but never in the fœtal. Occurring in the decidual cells of both zones, it increased and reached a maximum between the twelfth and sixteenth days[3] (Fig. 131); then it steadily diminished, and in the last week only a few granules were found scattered in the conglomerate masses of decidual cells. At the zone of separation, however, glycogen granules were still contained in decidual cells. Chipman also examined the fœtal liver. In it he found that glycogen appeared at the twenty-second day, and increased rapidly and steadily in amount till the end of pregnancy.

These results have for the most part been corroborated by chemical analyses carried out by the writer, working in collaboration with Dr. W. Cramer.[4] They determined quantitatively the glycogen of the maternal placenta, fœtal liver, and remainder of the fœtal body in an age-series of pregnant rabbits from the fourteenth day to the end of pregnancy. The maternal placenta was separated mechanically from the fœtal placenta, and each was investigated separately. The maternal part includes the two glycogenic areas, the region of the uterine sinuses and the zone of separation. The fœtal part includes the peninsulæ of decidual tissue which form the intermediary zone; the glycogen contained in it belongs wholly to these peninsulæ and represents the fraction most intimately related to the trophoblast. It may on that account be termed the *proximal* glycogen, while that of the maternal part is the *distal* glycogen. On

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[1] Bernard, "Sur une nouvelle fonction du placenta," *Comp. Rend. Acad. Sci.*, Paris, 1859.

[2] Godet, "Recherches sur la structure intime du placenta du lapin," *Dissert. Inaug. à la Fac. de Méd. de Berne*, Neuveville, 1877.

[3] It has been shown that the corpus luteum in the rabbit reaches its maximum about the same time. (See Hammond and Marshall, *Proc. Roy. Soc.*, B., vol. lxxxvii., 1914; and Hammond, *Proc. Roy. Soc.*, B., vol. lxxxix., 1917.)

[4] Lochhead and Cramer, "The Glycogenic Changes in the Placenta and the Fœtus of the Pregnant Rabbit," *Proc. Roy. Soc. London*, B., vol. lxxx., 1908.

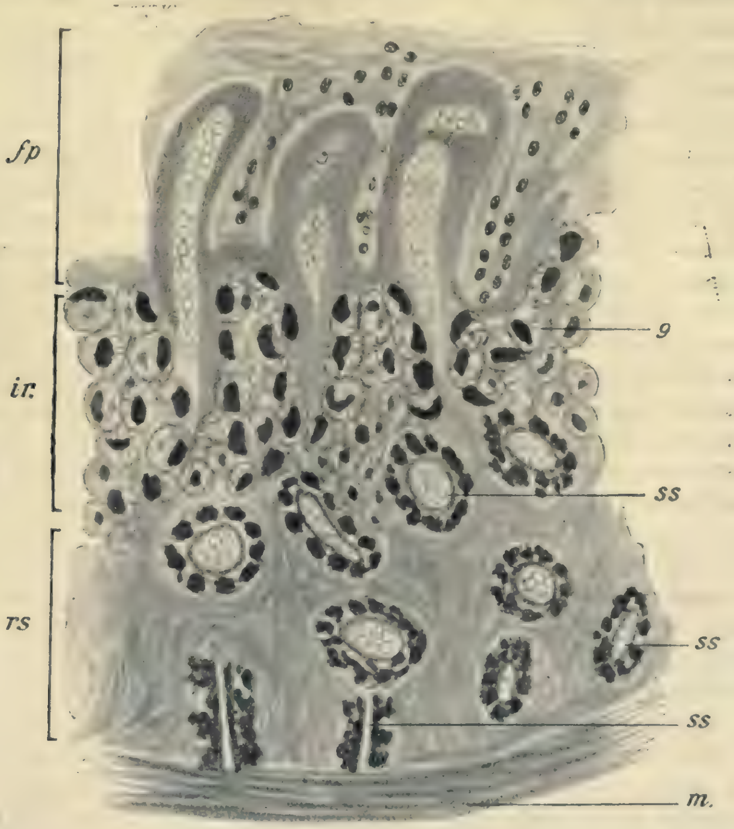

FIG. 131.—Glycogenic areas of the rabbit's placenta at the twelfth day of pregnancy. (Chipman.)

fp, Fœtal placenta, containing no glycogen; *ir*, intermediary region; *rs*, region of uterine sinuses; *ss*, uterine sinuses with perivascular sheaths of uninucleate cells rich in glycogen; *g*, glycogen granules in multinucleate cells; *m*, muscular wall immediately above which, at a later date, the zone of separation, containing glycogenic decidual cells, is differentiated.

the fourteenth day the distal glycogen forms over four per cent. of the weight of the maternal part, and it gradually increases till the eighteenth day, when it forms 5·5 per cent.; it remains nearly constant till the twenty-second day, and then there is a continuous decrease each day till the end of pregnancy. On the day before labour it amounts to slightly over one per cent., and practically the whole of it is situated at the zone of separation. This last is probably *not* destined for the fœtus.

The variations in the *proximal* glycogen are similar. At the twenty-ninth day there is no glycogen left in the intermediary region.

In the fœtal liver traces of glycogen are present at the eighteenth day, though none can be demonstrated histologically till four days later. Up to the twenty-fourth day the percentage gradually increases, but is still very small. Next day it rises for the first time above the glycogen percentage in the rest of the fœtal body, and then there is a rapid increase till, on the twenty-ninth day, half of the fœtal glycogen is stored in the liver. Hence it may be concluded that, although the liver contains glycogen in the earlier stages, a change occurs at the twenty-fifth day of pregnancy. Only then does it store more than its proportion of glycogen by weight, and thus may be said to be capable of carrying on the glycogenic function for the fœtus. Before that date the only store of glycogen available is contained in the maternal placenta. "The glycogen metabolism of the placenta and fœtus shows a regular succession of changes which proceed almost regardless of external conditions, and which are independent to a great extent of the glycogen metabolism of the mother" (Lochhead and Cramer).

There can be little doubt that the glycogen stored in the decidual cells is absorbed by the trophoblast. It is situated in the maternal peninsulæ which are surrounded by fœtal tissue, and it gradually decreases in amount while it increases in the fœtus. That none can be demonstrated in the trophoblast may be due to a transformation into sugar before it is absorbed. Glycerine extracts of both the maternal and the fœtal part of the placenta possess an enzyme which has a powerful hydrolytic action on glycogen. On the other hand, the enzyme action is markedly weaker, or absent altogether, in the placentæ of Ruminants, in which the glycogenic changes are known to be insignificant.

It is not easy to determine why such a complex mechanism is necessary if, as is stated by Cohnstein and Zuntz,[1] glucose passes from the maternal to the fœtal circulation by diffusion. But these investigators have only proved that it diffuses when a hyperglycæmia exists in the mother. Under similar conditions glucose passes into the urine and liquor amnii in man, but it does not pass normally.[1] Hence it has not been proved that the sugar of the maternal blood is diffused unchanged through the trophoblast. It is more probable that the transference of sugar is not effected by a purely physical process, since the serum of the fœtal rabbit contains lævulose, while the serum of the mother has none (Paton, Kerr, and Watson [2]).

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[1] Cohnstein and Zuntz, "Weitere Untersuchungen zur Physiologie der Säugetierfötus," *Pflüger's Arch.*, vol. xlii., 1888.

Between the glycogen metabolism and the growth of the fœtus there is a distinct relationship, which probably depends directly on the uses to which glycogen is put. Part of it is accounted for by the intense carbohydrate metabolism which proceeds in the fœtus (Bohr [3]). The glycogen, which is thus katabolised, furnishes thereby the energy necessary for the formation of new tissues, the "Entwicklungsarbeit" of Tangl.[4] The question arises whether glycogen also performs anabolic functions in the development of the fœtus. "The absence of glycogen from some of the growing fœtal tissues, and the fact that many of the tissues in which it is present do not contain even as much as the adult ones, leave little doubt that a definite formative power cannot be attributed to glycogen as such. On the other hand, the scarcity of glycogen in embryonic tissues does not necessarily justify the conclusion that glycogen does not take part in the building up of the tissues. It is well known that embryonic tissues are rich in mucin, which contains a large amount of a carbohydrate group in its molecule. Although glycogen as such has no formative power, it may yield one of the 'Bausteine' for the building up of the main protein body of fœtal tissues. In this connection it is interesting to consider the conditions in the hen's egg, which contains in itself the material of which the embryo is built up.[5] In the ovum carbohydrate as such is practically absent. At the same time all the protein substances of the white of egg are distinguished by the presence of a large amount of glucosamine in their molecule. Here the carbohydrate group has entered into the protein molecule, and correspondingly there is a scarcity of free carbohydrate."[6]

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[1] Even in the hyperglycæmia of diabetes the figures do not support the theory of the mere diffusion of glucose. Offergeld found 0·8 per cent. of sugar in the maternal blood, and 2·2 per cent. in the fœtal blood in diabetic coma ("Ueber das Vorkommen von Kohlehydraten im Fruchtwasser bei Diabetes," *Zeit. f. Geb. u. Gynäk.*, vol. li.).

[2] Paton, Kerr, and Watson (B. P.), "On the Source of the Amniotic and Allantoic Fluids in Mammals," *Trans. Roy. Soc. Edin.*, vol. xlvi., 1907.

[3] Bohr, "Die respiratorische Stoffwechsel des Säugetierembryos," *Skand. Arch. f. Physiol.*, vol. x., 1900. See also vol. xv., 1904.

[4] Tangl, "Beiträge zur Energetik der Ontogenese," *Pflüger's Arch.*, vol. xciii., 1903.

[5] Compare Emrys-Roberts, "A Further Note on the Nutrition of the Early Embryo, with Special Reference to the Chick," *Proc. Roy. Soc. London*, B., vol. lxxx., 1908.

[6] Lochhead and Cramer, *loc. cit.*

Protein Metabolism

In so far as the influence of the trophoblast on proteins has been investigated in the placenta of the rabbit, it may be considered here. It is generally accepted that colloid substances with large molecules, which are not adapted for diffusion, require a preliminary transformation, by which the size of the molecules is decreased before they can be taken up by the fœtal ectoderm. But the actual observations are against such a general statement. In the sheep the trophoblast can absorb not only hæmoglobin, a colloid, without any preliminary transformation, but even enormously larger masses of protoplasm in the form of cells. On the other hand, such hydrolysed products of albumen as albumoses and peptone are not present in the fresh placenta, nor can any extra-cellular proteolytic enzyme be extracted.[1] Hence there is no evidence of a placental digestion of proteins before their absorption by the trophoblast. Further, it has been shown, by means of the precipitin reaction, that if egg-albumen is injected into the mother some of it passes unchanged to the fœtus (Ascoli[2]). On the other hand, the proteins of ox-serum cannot be recognised in the fœtal blood, even when a considerable quantity is injected.[3] The reason appears to be that the proteins of ox-serum resemble more closely the normal serum proteins of the rabbit and are metabolised by the trophoblast, while egg-albumen cannot be utilised, and is passed on to the fœtal circulation unchanged. Hence it is probable that the normal proteins of the serum are also transformed by the trophoblast into a form suitable for the fœtus. The exact nature of the transformation is unknown, but it is not comparable with the hydrolytic processes which occur in the intestine.

Respiration

According to Bohr,[4] the fœtal rabbit absorbs slightly more oxygen and gives off slightly more carbonic acid per kilogram per hour than the mother. Hence the intensity of the metabolic reactions is slightly greater in fœtal life. This is directly opposed to the views held by Pflüger on theoretical grounds, and by Cohnstein and Zuntz[5] from their experimental results. The second result of Bohr's experiments has been already mentioned, viz. that in that part of the metabolism which is evidenced by the respiratory exchange, the energy arises from carbohydrates. He arrived at this conclusion as a result of determining the respiratory quotient[1] in pregnant rabbits and guinea-pigs before and during the compression of the umbilical cord, the difference representing the respiratory exchange in the embryo. He found that the quotient in such cases was unity, thus showing that the substance oxidised in the developing embryo must have been a carbohydrate. Bohr supposed that the energy liberated by the combustions, which in the adult is dissipated largely under the form of heat radiated and water evaporated from the surface of the body, is in the fœtus used for the increase and maintenance of the newly formed tissues; in other words, "the reactions of synthesis, which are so numerous during development, are endothermic or heat-absorbing, and they borrow the heat from other simultaneous exothermic actions,"[2] in this case the oxidation of carbohydrates.

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[1] Lochhead, "On the Transmission of Nitrogenous Compounds from Mother to Fœtus," *Trans. Obstet. Soc. Edinburgh*, vol. xxxiii., 1907-08.

[2] Ascoli, "Passiert Eiweiss die placentare Scheidewand?" *Zeit. f. physiol. Chem.*, vol. xxxvi., 1902. This has been confirmed by the writer and Dr. W. Cramer (see reference, note [1].

[3] Lochhead, *loc. cit.*

[4] Bohr, *loc. cit.*

[5] Cohnstein and Zuntz, "Untersuchungen über das Blut, den Kreislauf und die Atmung der Säugetierfötus," *Pflüger's Arch.*, vol. xxxiv., 1884.

Ferments and Vital Staining

Frank[3] has carried out an investigation to determine whether any differences existed in the ferment content of the functionating as compared with that of the non-functionating placenta. His results were mostly negative, no definite evidence being afforded either for or against the view that the placenta acts as an accessory organ of metabolism to the fœtus. The experiments were mainly upon the rabbit.[4] The ferments investigated were amylase (or starch hydrolysing ferment), lipase (fat splitting), and erepsin (hydrolysing peptone to amino-acids), and their respective contents were determined by appropriate tests. The amylase content was the same or less than that of the maternal blood, the lipase rather more, and the ereptic content considerably more. The fœtal blood contained less ferments than the maternal. Neither fœtal nor maternal blood showed any changes in ferment strength in relation to the progress of pregnancy. The organs of large fœtuses have high ferment values, sometimes higher than those of the corresponding organs in the mother. The investigation upon "vital staining," in which the acid stain "trypanblau" was injected subcutaneously into pregnant rabbits and guinea-pigs, was carried out to supplement the research upon the ferments. The evidence obtained, according to Frank, favoured the view that the placenta is a passive organ of exchange rather than an active organ of metabolism. The uterus was found to take the stain first; next the yolk membrane, and last the placenta. The kidney and liver in the fœtuses readily absorbed the dye but other organs were affected. Goldmann[1] has also investigated the effects of vital staining and traced the paths by which the dye (trypan or pyrrol blue) enters the fœtus, and has made a careful study of the behaviour of the placenta towards vital stains. Of especial interest is the marked reaction of the wandering connective tissue cells ("pyrrol cells") to the vital stain.

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[1] The respiratory quotient is the ratio of CO_2 discharged to O_2 absorbed, that is, the fraction $\frac{CO_2}{O_2}$. For an exclusively carbohydrate food this is unity; for a fat or protein, less than unity. For a discussion of the subject in relation to fœtal metabolism see Feldman, *Principles of Ante-Natal and Post-Natal Child Physiology*, London, 1920. See below, p. 504.

[2] See Richet's *Dictionnaire de Physiologie*, vol. vi., Article "Fœtus."

[3] Frank, "An Experimental Study of the Placenta, etc.," *Surg., Gyn. and Obstet.*, November 1912.

[4] The animals used were six rabbits, three guinea-pigs, two cats, and a bitch.

Wislocki[2] found that when trypan or pyrrol blue are injected intravenously into the pregnant rabbit, as with the guinea-pig, mouse, and rat, traces of the colloid may pass into the amniotic fluid, and even stain the fœtus. In the case of the cat, however, they only reach the placenta and are stored in the form of granules in the chorionic ectoderm. Wislocki concludes, therefore, that the placenta of the carnivore is less permeable than that of the rodent. Colloidal dyes injected into the amniotic cavity of the cat and guinea-pig in later pregnancy are absorbed through the gastro-intestinal and respiratory tracts and by diffusion through the amniotic membrane. The fœtus becomes vitally stained, but none of the colloidal material passes into the maternal circulation. Wislocki also administered intravenously a solution of India ink to pregnant rabbits and other animals, and found that neither the chorionic epithelium nor the placental endothelium could absorb or phagocytise granules as coarse as this, and the placental and fœtal membranes were entirely unstained. Phenolsulpho-naphthalein injected into the fœtal peritoneal cavity is absorbed by the blood-stream, passes to the placenta, and thence to the maternal circulation and kidneys; it is also excreted by the fœtal kidneys. Trypan blue (a less diffusible colloid), when similarly injected, vitally stains the fœtus, is excreted by the fœtal kidneys, but does not traverse the maternal placenta and enter the maternal circulation.

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[1] Goldmann, "Neue Untersuchungen über äussere und innere Sekretion des Gesunden und Kränken Organismus im Lichte der 'Vitalen Färbung,'" Tübingen, 1912; reprinted from *Beitr. zur klin. Chir.*, vol. lxxviii., 1912. This memoir, which contains many references to literature, includes also a detailed account of the investigation of the glycogen, fat, iron, and hæmoglobin absorption through the placenta by microchemical methods. The methods of vital staining have been taken advantage of in their application to the study of the cell nucleus by Kite and Chambers ("Vital Staining of the Chromosomes and the Function and Structure of the Nucleus," *Science*, vol. xxxvi., (November) 1912.

[2] Wislocki, "Experimental Studies on Fetal Absorption," I. to IV., *Contributions to Embryology*, vols. xi. and xiii., Carnegie Institute (Washington) Publication 276, 1920-21. See also *Johns Hopkins Hospital Bull.*, vol. xxxii., 1921; and *Anat. Rec.*, vol. xxi., 1921.

Mouse.—The fertilised ova of the mouse reach the uterine cavity on the third day, and segmentation is completed one day later. The zona pellucida has by this time disappeared, and fixation of the ovum to the uterus can be quickly attained. Each blastocyst comes to rest in an anti-mesometrial groove. At first spherical, it becomes ovoid on the sixth day, with the long axis perpendicular to the long axis of the uterus. One pole is turned towards the mesometrium and is composed of several layers of cells, while the opposite pole is single-layered. It is nourished by the glandular secretion, and perhaps also by a transudate, in which, however, leucocytes are not present.

The connective tissue of the mucosa shows a thickening at the point where a blastocyst rests. The epithelium degenerates as the result of contact with the fœtal ectoderm (Duval[1]), or of pressure by the proliferated connective tissue cells which interferes with the nutrition of the epithelium (Burckhard[2]), More probably it is not mechanical, as the change begins first at the mouth of the groove, *i.e.* at the point of first contact with the ovum (Kolster[3]). In the cells the chromatin clumps on the inner surface of the nuclear membrane, the cell boundaries disappear, and a symplasma is formed which later becomes broken up into nuclear and cellular fragments. Fat globules, which are present in the epithelium of the non-pregnant uterus, are found in the detritus and also in the fœtal ectoderm.

With the destruction of the epithelium appears the first sign of decidual formation. The connective tissue cells increase in size and displace the glands; the capillaries dilate irregularly, and at places form sinuses.

On the sixth day the *ectoplacental cone* is formed by a proliferation of the ectoderm at the mesometrial pole of the blastocyst. It plugs the opening between the crypt and the lumen of the uterus. At the same time the lips of the crypt are gradually brought nearer to each other by the swelling of the tissues, and at the end of the seventh day they fuse and cover the ectoplacenta. In this way the ovum is completely shut off in a decidual cavity, the "Eikammer," from the uterine lumen. The roof of the chamber forms the primary decidua reflexa, and it is gradually thickened by a decidual deposit. In it new blood-vessels are developed, and they form a specially rich vascular network.

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[1] Duval, "Le Placenta des Rongeurs," *Jour. de l'Anat. et de la Phys.*, 1891.

[2] Burckhard, "Die Implantation des Eies der Maus in die Uterinschleimhaut," *Arch. f. mikr. Anat.*, vol. lvii., 1901.

[3] Kolster, "Zur Kenntnis der Embryotrophe beim Vorhandensein einer Decidua Capsularis," *Anat. Hefte*, vol. xxii.

By this time the blastocyst has become tubular in shape, and it shows an *inversion of the germinal layers* (Fig. 132). In the earlier stage a cavity appears in the inner mass of cells. The roof of the cavity becomes thickened to form the "Träger" or ectoplacental cone, which is at first cylindrical and later conical, with its base resting on the mesometrial pole of the ovum. By its inward growth it shoves before it the floor of the inner mass consisting of epiblast and hypoblast. In this way an invagination is produced in the tube with the epiblast internal to the hypoblast. Hence the germinal layers are said to be inverted.

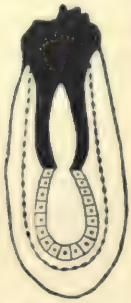

Fig. 132.—Inversion of the germinal layers in the blastodermic vesicle of the mouse. The trophoblast becomes greatly thickened and invaginated, pushing the formative epiblast before it. The whole blastocyst assumes a tubular shape, and the hypoblast appears to be external to the epiblast. Trophoblast represented by continuous black lines or masses: entoderm by interrupted lines: embryonic ectoderm by epithelial cells. (T. H. Bryce, in *Quain's Anatomy*, Longmans.)

Blood is regularly found in the implantation cavity. It completely surrounds the ovum, and reaches irregular spaces in the ectoplacenta which communicate with the surface. At this time, however, there are no fœtal vessels near the cone, and the blood in its meshes may be of use only for its own nutrition. On the other hand, the thin trophoblast of the wall of the invaginated yolk-sac is partly vascularised by vitelline vessels, by means of which the nutriment absorbed from the blood effusion may reach the embryo or be stored in the yolk-sac. In the trophoblast itself the hæmoglobin of laked corpuscles and its derivatives are present (Jenkinson[1]), and the contents of the umbilical vesicle are "not yolk, but another nutritive substance which the ovum, in the absence of yolk, takes from the maternal tissues, viz. hæmoglobin" (Sobotta[2]).

The decidual cavity is at first small and ovoid, and has a thick wall. As it grows, the lumen of the uterus is obliterated, and at its point of contact with the mesometrial wall the epithelium of the latter disappears. Thereafter the two layers fuse, and at the point of fusion the placenta is developed. The lumen of the uterus is later re-established, as in the guinea-pig (see Fig. 137), at the floor of the decidual cavity. Hence the primary decidua reflexa forms the serotina, and a secondary reflexa is formed, which is recognisable till the twentieth day of pregnancy.

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[1] Jenkinson, "Observations on the Histology and Physiology of the Placenta of the Mouse," *Tijd. Nederl. Dierk.*, Ver. ii., Dl. vii.

[2] Sobotta, "Die Entwicklung der Maus," *Arch. f. mikr. Anat.*, vol. lxi., 1903.

The increase in size of the implantation cavity is accompanied by a thinning of its wall. According to Duval this is a mechanical process, since the cells do not increase in number, but it is probably more complicated. On the inner surface of the decidua giant-cells appear around the ovum, and they are phagocytic (Fig. 133). Duval stated that each was derived from a cell of the fœtal ectodermal wall of the yolk-sac, and later from a cell of the ectoplacental cone. As they increase in number, they form a distinct layer, two to five cells in depth, between the yolk-sac and the wall of the implantation

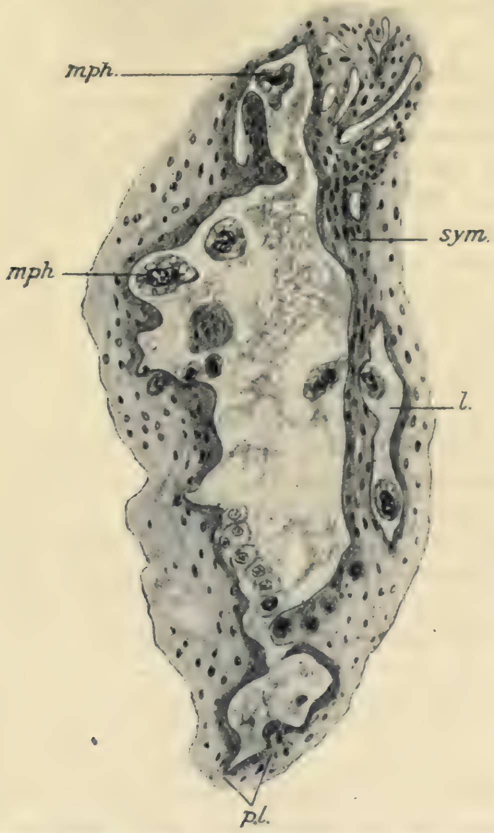

Fig. 133.—Longitudinal section of the implantation cavity of the field-mouse about the eighth day of pregnancy. (From Disse's "Die Vergrösserung der Eikammer bei der Feldmaus (*Arvicola arvalis*)," *Arch. f. mikr. Anat.*, vol. lxviii., 1906.)

pl, Placental pole; *mph*, macrophags or giant-cells; *sym*, uterine symplasma; *l*, blood lacuna.

cavity, and some wander into the decidua and lie singly or in groups. In their interior degenerating leucocytes are frequently seen. Sobotta also stated that they were fœtal in origin, and helped to fix the ovum and erode maternal capillaries. More recently Kolster has brought forward evidence from their histological appearance that they are transformed decidual cells, and this is strongly supported by Disse's investigations on the field-mouse,[1] in which the giant-cells are found before the ovum has become embedded, and the first to appear are at an appreciable distance beneath the surface epithelium. A second series of smaller size appears later in the lumen and wall of the implantation cavity. Jenkinson also recognised two groups, but assigned to them different origins, fœtal in the "Eikammer" and maternal in the decidua.

All authorities agree that they are phagocytic. The tissue around them undergoes fatty degeneration, and in their interior may be seen remnants of connective tissue and endothelial cells and fat globules. Many capillaries are ruptured, and red and white blood corpuscles are also absorbed. Such an absorption of maternal tissue by the giant-cells leads to an increase in the size of the implantation cavity and a thinning of its wall (Disse). In spite of their abundant supply of nutriment, their life-history is short. No cell-divisions occur, and soon they degenerate. Their contents are absorbed by the trophoblast, and their protoplasm shrinks to form a rim around the nucleus. Later still their remnants are also absorbed.

The allantois in the mouse is a solid mass of mesoderm with no entodermal cavity. Growing out from the posterior end of the embryo, it projects into the extra-embryonic cœlom, and on the eleventh day fuses with the mesoblast of the ectoplacental cone. After this the ovum again becomes spherical. The circulation in the decidua reflexa diminishes, and gradually more and more of the nutriment is conveyed to the embryo by the allantoic vessels. At the same time the allantoic trophoblast increases in thickness, and its lacunæ become more numerous and complicated. Into its mass, in which the circulation of maternal blood is now established, the vascular mesoblast projects at intervals, and breaks it up into segments. The glands take no part in the formation of the placenta. Their ducts do not even act as guides to the advancing edge of the trophoblast, as in the rabbit. They are completely displaced by the rapid formation of decidual tissue, and their remnants are absorbed by the giant-cells. Hence the embryotrophe contains no glandular secretion.

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[1] Disse, "Die Vergrösserung der Eikammer bei der Feldmaus," *Arch. f. mikr. Anat.*, vol. lxviii., 1906.

At this time the nutritional conditions are essentially the same as in the rabbit. The trophoblast shows two layers, plasmodiblast and cytoblast, which intervene, along with mesoblastic cells and the walls of the villous capillaries, between the two blood-streams. The subsequent changes are all in the way of producing an increased surface of contact with maternal blood, and lessening the thickness of tissue between it and the fœtal circulation.

In the mouse the decidual cells contain glycogen. According to Driessen,[1] its distribution in the placenta of the white mouse before mid-term is the same as in the rabbit. It is in great abundance in the decidual cells, especially in the boundary layer between the maternal and fœtal tissues. No glycogen is found in the maternal endothelium or in the fœtal placenta. Jenkinson[2] has studied the distribution of glycogen throughout the whole period of gestation in the mouse. It appears first in the cells which overlie the ectoplacenta, and increases in amount till the twelfth day, when the mesoblastic processes are just beginning to project into the trophoblast. Then the decidual cells are disintegrated and the glycogen granules are mixed with the detritus. Hence the life-history of the maternal glycogenic tissue is shorter than in the rabbit. But in the mouse glycogen again makes its appearance in the trophoblast which is most directly in contact with the maternal blood, *i.e.* the part not penetrated by the allantoic capillaries. It lies in oblong ectodermal cells, which gradually encroach on and occupy the space previously occupied by the maternal glycogenic cells down to the muscularis. Here the glycogen remains till the end of gestation.[3]

"There can be no doubt that this tissue holds in reserve a store of food material for the use of the embryo. As sugar the glycogen passes into the maternal vessels and into the lacunæ, and so is absorbed by the fœtal capillaries. When the glycogen is used up the cells collapse, and their collapse may be a factor in determining the moment of parturition, since it is across this layer that the placenta breaks away. The trophoblastic is much more voluminous than the maternal glycogenic tissue ever was" (Jenkinson[4]).

According to Kolster, a considerable amount of fat appears in the decidua, in which the connective tissue and endothelial cells undergo a fatty degeneration in the proximity of the giant-cells. No observations have been made regarding the metabolism of iron-containing substances.

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[1] Driessen, "Ueber Glykogen in der Placenta," *Arch. f. Gynäk.*, vol. lxxxii., 1907.

[2] Jenkinson, *loc. cit.* See also *Brit. Med. Jour.*, 1904.

[3] Whether the differences in the distribution of the placental glycogen in the rabbit and the mouse during the later stages of pregnancy exist in reality, or depend only on differences of interpretation, requires further investigation.

[4] Jenkinson, *Vertebrate Embryology*, Oxford, 1913.

Guinea-Pig.—In the guinea-pig the ovum is again completely surrounded by decidua. Reichert[1] was the first to notice that the ovum lay in a special cavity, "a little nest." Bischoff[2] stated that the nest was only temporary, and the ovum again appeared in the uterine cavity, only that part of the nest remaining which formed the placenta. After a long interval this was proved to be wrong by Reichert[3] and Hensen.[4]

The fertilised ovum reaches the uterus as a morula or early blastocyst, surrounded by the zona radiata. On the seventh day the zona disappears and embedding begins, but even before this, according to von Spee,[5] the ovum is fixed by processes which extend from the cells of the implantation pole through the zona and come into direct metabolic relationship with the epithelial cells. As in the mouse, the blastocyst remains small, about one-tenth of a millimetre in diameter. At its point of contact with the mucosa, the epithelium is rapidly eroded, and absorbed along with its fat globules by the fœtal ectoderm. At the same time changes occur in the deeper layers. In

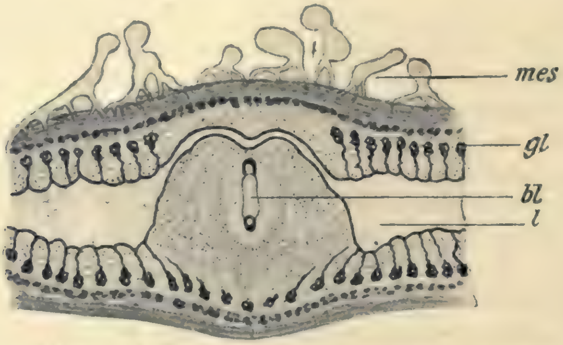

FIG. 134.—Longitudinal section of the uterus and implantation cavity of the guinea-pig. (From Duval's "Le Placenta des Rongeurs," *Journ. de l'Anat. et de la Phys.*, 1892.)

mes, Mesometrial border ; *gl*, uterine glands ; *l*, uterine lumen ; *bl*, blastodermic vesicle.

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[1] Reichert, "Ueber die Bildung der hinfälligen Häute der Gebärmutter," *Müller's Arch.*, 1848.

[2] Bischoff, *Entwicklung des Meerschweinchens*, 1852.

[3] Reichert, "Beiträge zur Entwicklungsgeschichte des Meerschweinchens," *Abhandl. d. Akad. d. Wissensch. zu Berlin*, 1861.

[4] Hensen, "Beobachtungen über die Befruchtung und Entwicklung des Kaninchens und Meerschweinchens," *Zeit. f. Anat. u. Entwick.*, vol. i., 1866.

[5] Von Spee, "Die Implantation des Meerschweincheneies in die Uteruswand," *Zeit. f. Morphol. u. Anthropol.*, vol. iii., 1901.

the non-pregnant uterus two layers are present, a sub-epithelial layer of embryonic connective tissue cells interrupted only by capillaries and glands, and a deeper, more reticulate layer. Before the ninth day of pregnancy, no very marked changes occur in the mucosa. Some of the cells show mitoses, the blood-vessels are full, and a few red blood corpuscles may lie between the cells, and also in the fœtal ectoderm. During the penetration of the epithelium by the trophoblast, some of the superficial connective tissue cells enlarge. Their nuclei stain more deeply, and the protoplasm of adjacent cells fuses to form a symplasma. The degenerated tissue in its immediate neighbourhood is absorbed by the ectoderm, and the blastocyst thus comes to lie in the substance of the mucosa (Fig. 134). According to von Spee, the destruction of uterine tissue is effected entirely by a biochemical process; there is no evidence of absorption of formed elements by phagocytosis.

Round the periphery of the necrotic zone lies a thick layer of large fœtal cells, the two together forming the "Implantationshof." Later the symplasma degenerates further. The nuclei shrink and lose their chromatin, and the protoplasm becomes fibrillated and granular. Vacuolations appear in the mass, and coalesce to form a space round the ovum filled with clear fluid. In this way the implantation cavity is excavated till it is limited externally by the large cells. Outside it the decidual cells around the vessels survive, while the rest are transformed to a symplasma and absorbed. Hence the wall is sinuous. The dips are, however, filled up in part by newly formed tissue resembling granulation tissue. It encapsules the necrotic zone, and may be looked on, as in the rabbit, as a defence against the advancing ectoderm (see p. 403).

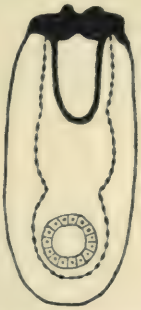
FIG. 135.—Blastodermic vesicle of the guinea-pig, showing inversion of the germinal layers. The blastocyst is tubular, and the formative cell-mass is invaginated as in the mouse, but the thickened trophoblast is not invaginated to so great an extent as in Fig. 132, and the connection between them is lost. Hence the roof of the amnio-embryonic cavity is independent of the trophoblast. (T. H. Bryce in *Quain's Anatomy*, Longmans.)

By this time the ovum has become tubular, with its long axis perpendicular to the long axis of the uterus. It exhibits, as in the mouse, an inversion of the germinal layers, but in the guinea-pig the amnio-embryonic vesicle is closed and separates the thickened trophoblast from the embryonic ectoderm (Fig. 135). With the growth of the blastodermic vesicle, the roof of the implantation cavity projects into the lumen of the uterus, and in time obliterates it by coming in contact and fusing, at the tenth day, with the mesometrial mucosa (Fig. 136). Here also the cellular tissue has developed at the expense of the glands, and the surface epithelium disappears. At the fifteenth day the lumen reappears anti-mesometrially (Fig. 137). Thus a secondary decidua reflexa arises which rapidly thins and becomes vacuolated in its inner half by a loss of tissue. The cause of the tissue excavation is uncertain; it may be brought about by the large cells which, according to von Spee, are fœtal and form a third layer of the trophoblast outside the plasmodiblast, and the disintegrated products are probably absorbed by the ovum. At the same time the vessels which penetrate the necrotic zone are opened, and blood is effused into the implantation cavity.

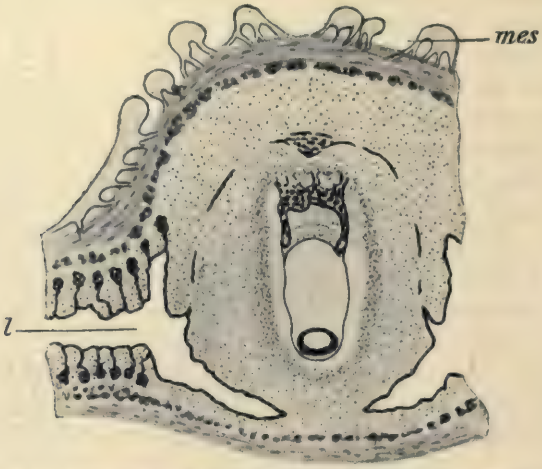

FIG. 136.—Implantation cavity of the guinea-pig. (Duval.) *mes*, Mesometrial border; *l*, uterine lumen.

The placenta develops, as in the mouse, mesometrially. The allantois consists of a tubular passage in the body wall and a solid extra-embryonic stalk of mesoderm. It projects into the cœlom and gradually extends, and becomes applied to the mesoblast underlying the thickened part of the trophoblast, in the spaces of which a circulation of maternal blood is established. The trophoblast continues to attack and absorb maternal tissue and blood, and to advance more deeply into the decidua, while at the same time it is penetrated on the embryonic side by outgrowths of mesoblast containing branches of the allantoic vessels. The tissues intervening between the maternal and fœtal blood-streams are entirely fœtal; they gradually thin with the progress of gestation and the continued branching of the mesodermal villi.

Glycogen is contained in the decidual cells, but its variations have not yet been investigated. It is of interest historically that oxyhæmoglobin was demonstrated first in the umbilical vein of a fœtal guinea-pig by Schmidt.[1] The amounts of oxygen absorbed and carbonic dioxide excreted are the same, weight for weight, as in the fœtal rabbit (Bohr). (See above, p. 464.)

Fat is widely distributed in the fœtus, and Hofbaur[2] has shown that the fatty acid of a fat ingested by the mother guinea-pig may be transmitted across the placenta to the fœtuses. The mother was fed on coco-nut oil which consists largely of triglycerides of laurinic and myristinic acids, and considerable quantities of laurinic acid were afterwards found in this guinea-pig's fœtuses (see p. 543).

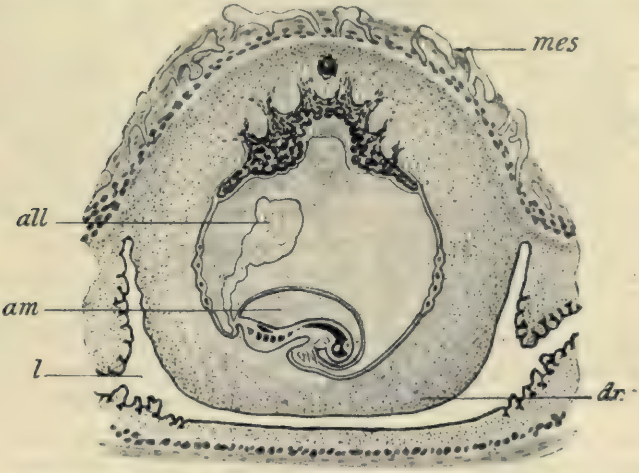

Fig. 137.—Implantation cavity of the guinea-pig. (Duval.)
mes, Mesometrial (placenta) border ; *l*, lumen of uterus, re-established anti-mesometrially ; *d.r.*, decidua reflexa ; *all*, allantois ; *am*, amnion.

Beaver.—The connecting membrane, or "Haftstiel," and the part it plays in this animal have already been referred to (p. 423). Another noteworthy feature is the abundance of erythrocytophagous and leucocytophagous cells. There is no bleeding into the uterine cavity, but the maternal capillaries, which are very numerous, abut upon implanted megalokaryocytes and discharge the red corpuscles directly into the trophoblast. The extravasated erythrocytes are all ingested by megalokaryocytes. Migrating leucocytes in large numbers are also absorbed by the large phagocytic cells.

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[1] Schmidt, "Sauerstoffhämoglobin in Fötusherzblut," *Cent. f. d. med. Wiss.*, 1874, No. xlvi.

[2] Hofbaur, *Grundzüge einer Biologie der Menschlichen Plazenta*, Leipzig, 1905.

The trophoblast of the beaver in the preplacental stage is at the areas of attachment not more than one layer in thickness. It does not send processes to any depth into the mucosa, but has a flat insertion upon the decidual surface, the maternal capillaries pressing towards the trophoblast rather than otherwise. Whenever the uterine epithelium is displaced by the ob-placental trophoblast it disappears without forming a syncytium. The uterine epithelium probably becomes necrotic in advance of the trophoblastic growth, and the latter does not destroy the epithelium which is normal at the borders of the decidual surface.[1]

INSECTIVORA.—The importance ascribed to the placentation in Insectivora has already been referred to (see p. 409). The hedgehog, shrew, mole, and *Tupaia* have been most fully investigated.

Hedgehog.—In the hedgehog (*Erinaceus europæus*), the zona pellucida disappears early, before the expansion of the hypoblast, which, as in man, forms a closed vesicle. The chronology of embedding is not yet known. In the earliest stage examined by Hubrecht,[2] the blastocyst was 0·22 of a millimetre in diameter. The outer wall was several layers thick all round its circumference, and spaces were already present in it. At a slightly later stage the blastocyst grows rapidly and the epiblast is reduced to a single layer, with numerous villiform processes at intervals, except for a thickened knob which represents the future germinal area. Even now the name *trophoblast* may be given to the single layer of epiblast with its projections, excluding the thickened knob which is *formative* and gives rise to the embryonic ectoderm and the lining of the amniotic cavity. The mesoblast, as yet one-layered, which extends between the trophoblast and hypoblast, consists of an attenuated somatic part which forms with the trophoblast the *diplo-trophoblast*,[3] and a splanchnic part which forms blood-vessels and blood.

The early blastocyst comes to rest, as in the mouse, in an anti-mesometrial furrow of the mucosa. It is not yet determined whether any changes occur previously in the uterus; but at least, soon after the blastocyst has taken up its position, there is a great cell-proliferation in the stroma of the floor and walls of the furrow, not perivascular as in the rabbit, but sub-epithelial. Along with this decidual formation, the lumina of the glands are closed, and their epithelium gradually disappears, perhaps by the influence of the trophoblast. The capillaries are distended and new vessels are formed. This distension is at first most marked in the lips and sides of the groove, and small superficial hæmorrhages occur, which detach the epithelium at places. The tissue fluids also exude, and, along with the blood and desquamated epithelium, form a coagulum around the ovum. Part of it shuts off the entrance of the furrow from the uterine cavity.

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[1] Willey, "The Blastocyst and Placenta of the Beaver," *Quar. Jour. Micr. Science*, vol. lx., 1914.

[2] Hubrecht, "The Placentation of *Erinaceus europæus*," *Quar. Jour. Micr. Science*, vol. xxx., 1889.

[3] Hubrecht restricts the term *chorion* to *Tarsius* (a lemur), monkeys, apes, and man (see p. 490).

The epithelium of the crypt, after a preliminary proliferation such as Robinson describes in the mouse and rat, degenerates entirely, part being stripped off by extravasated blood and part yielding to the influence of the fœtal ectoderm. Its remnants and the other constituents of the coagulum probably furnish pabulum for the ovum. The development of the decidua proceeds rapidly, and the swollen lips of the groove fuse together to complete the implantation cavity. The trophoblast is now in contact with decidual tissue, of which the innermost zone consists of a stratified layer of fusiform cells, best marked in the allantoic region (Fig. 138). Whether they are maternal or fœtal in origin is not yet determined. They persist for a time, but disappear when the endothelial proliferation occurs. Around the groove the tissue becomes looser by an increase in the size of the newly formed blood-spaces. The

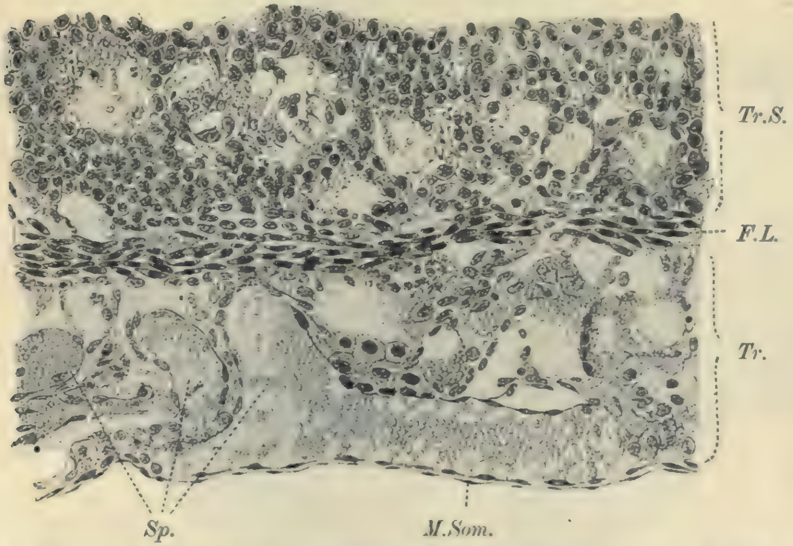

Fig. 138.—The allantoidean diplo-trophoblast of *Erinaceus*. (From Hubrecht's "The Placentation of *Erinaceus europæus*," *Quar. Jour. Micr. Science*, vol. xxx., 1889.)

Tr.S., Trophospongia; *Tr.*, trophoblast; *F.L.*, layer of fusiform cells; *Sp.*, spaces in trophoblast; *M.Som.*, thin layer of somatic mesoblast.

endothelium lining them is swollen and deep, and the cells bulge into the lumen. Near the ovum the endothelium proliferates and forms an enormous cell-mass, the *trophospongia*,[1] interposed between the blastocyst and the unaltered decidua. The trophoblast with its lacunæ, and the trophospongia with large blood-sinuses together form the *trophosphere*, which, along with the maternal blood, represents an effective nutritional arrangement for the embryo before the vitelline or allantoic circulation is established (Fig. 139). Many of the blood-spaces are ruptured, and the blood pours out into the lacunæ of the trophoblast, and circulates through them before returning into the maternal veins. At this stage the trophospongia is separated from the external decidua by rows of fusiform cells.

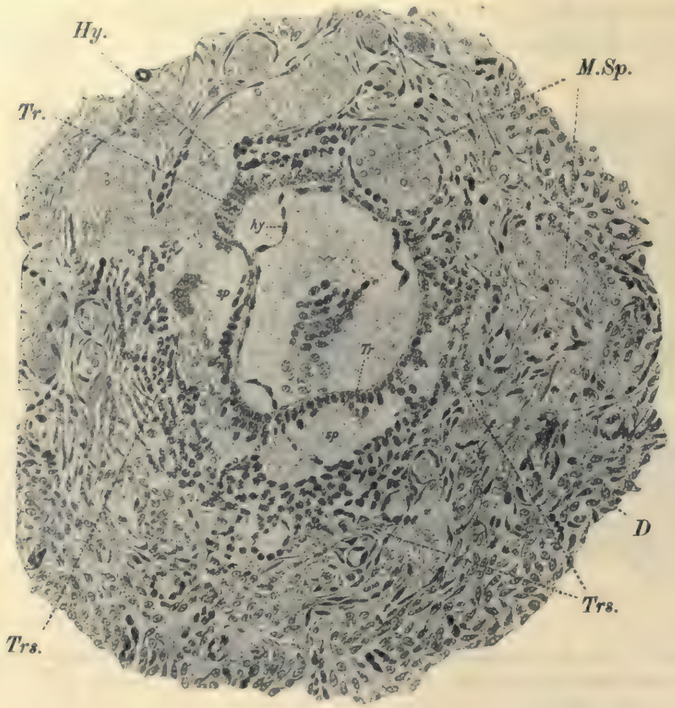

Fig. 139.—Section *in situ* of the ovum of *Erinaceus* (Hubrecht).
Hy., Hypoblast; *Tr.*, trophoblast; *sp.*, spaces in the trophoblast, communicating with the maternal blood-spaces (*M.Sp.*); *D.*, decidua; *Trs.*, trophospongia.

As in the mouse, in which, however, the trophospongia is derived from connective tissue cells instead of endothelium, giant-cells appear. They lie between the trophospongia and the fusiform cells, and they are first seen at the time of the appearance of the embryonic mesoblast. In their interior are contained fragments of red blood corpuscles and decidual cells. Hence they are called *deciduofracts* by Hubrecht (Fig. 140). Externally the circular layers of fusiform cells form sheaths round some of the endothelium-lined vessels. The line of union between the giant-cells and the external decidua is irregular, and the decidual tissue is fibrillar and reticulate.

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[1] "The trophospongia is a maternal cell-proliferation specially intended for the fixation of the blastocyst. It shows a different histological evolution in different genera" (Hubrecht).

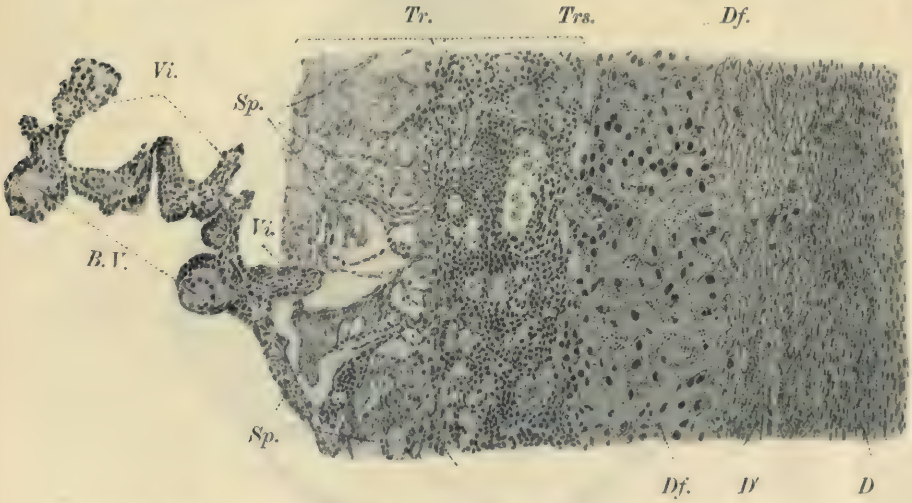

Fig. 140.—The extension of the yolk-sac against the lacunar trophoblast in *Erinaceus* (Hubrecht). The yolk-sac is to the left of the figure, and its villi (*Vi.*) and blood-vessels (*B. V.*) are well seen.

Tr., Trophoblast; *Trs.*, trophospongia; *Df.*, layer of deciduofracts; *D.*, decidua, of which the inner layer (*D'*) has assumed a more reticulate aspect; *Sp.*, spaces in trophoblast.

These appearances indicate an erosion and absorption of the maternal tissue. The deciduofracts are probably derived from the maternal trophospongia (Hubrecht[1]). After a short life-history they dwindle and are themselves absorbed.

With the changes in the mucosa, changes also take place in the trophoblast. After the thinning already mentioned, its cells increase in number. They grow in strands, leaving spaces between them like the meshes of a net, and in the spaces maternal blood circulates. In this respect the hedgehog differs from the Rodents, in which the proliferation of the trophoblast is confined to the allantoic region. In the hedgehog the proliferation occurs even in the omphaloidean region, which is vascularised by the area vasculosa. Here the vacuolated trophoblast is gradually interlocked with vascular processes of the mesoblast, and yolk-villi, containing branches of the vitelline vessels, are developed. The omphaloidean placenta thus formed embraces about one-half of the circumference of the blastodermic vesicle. With the union of the allantois and diplotrophoblast, the circulation in the decidua reflexa decreases, and it and the trophoblast in contact with it become membranaceous. They project into the uterine cavity and obliterate its lumen by meeting, but not fusing with, the mesometrial part of the uterine mucosa. As in the bat, the circulation in the yolk-sac never ceases entirely during pregnancy.

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[1] Hubrecht now considers that the deciduofracts are of fœtal origin, and represent the outermost layer of the trophoblast. See p. 496, footnote. Also compare Graf v. Spee's description of the trophoblast of the guinea-pig (see p. 473), and Bryce and Teacher's of that of man (see p. 496).

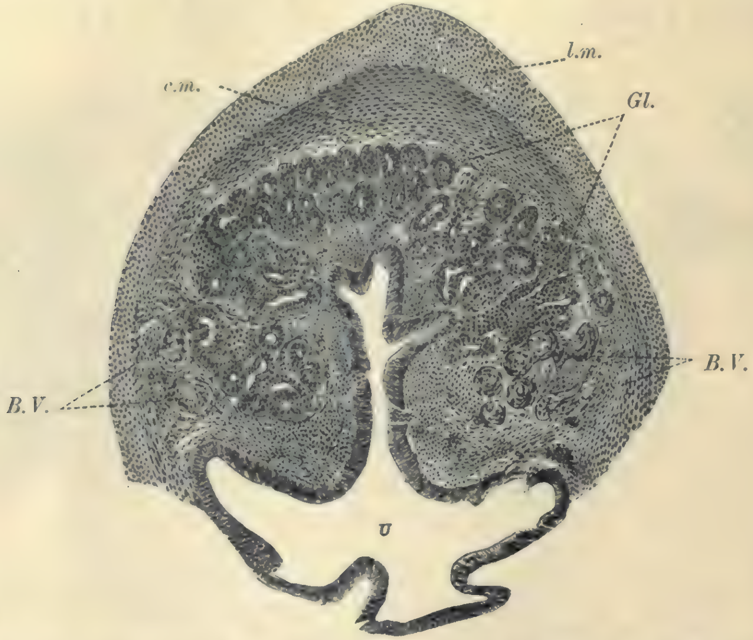

FIG. 141.—Transverse section through the uterus of *Sorex* at a stage when the blastocysts are still in the oviducts. The coiled uterine glands (*Gl.*) are massed together in the anti-mesometrial regions. The uterine lumen (*U*) is more or less ⊥-shaped. (From Hubrecht's "The Placentation of the Shrew," *Quar. Jour. Micr. Science*, vol. xxxv., 1894.)

B.V., Blood-vessels; *c.m.*, circular muscle; *l.m.*, longitudinal muscle.

The changes in the allantoidean trophoblast are of the same kind, but they occur later. It occupies a discoid area as in Rodents, but it is on the anti-mesometrial side, *i.e.* the primary decidua reflexa is permanent. The lacunar spaces in it are more complicated than in the omphaloidean trophoblast, and their walls bulge towards the embryo and interlock with vascular projections of the allantois. Hence the villi have a complete trophoblastic covering. The extremity of each villus is attached to the maternal decidua by strands of trophoblastic cells. The allantoidean trophospongia develops like the omphaloidean, but it retains its thickness later in pregnancy. The deciduofracts remain distinct to the end, though they partly degenerate. Hence it is probable that during the whole, or nearly the whole, of pregnancy they exercise a phagocytic action on the maternal tissues, and store nutriment which they give up to the embryo in a way as yet unknown.

Shrew.—In the shrew (Hubrecht[1]) the method of embedding is centric, and no decidua reflexa is formed. The yolk-sac placenta is not so well developed as in the hedgehog.

The attachment of the blastocyst is modified, as in Ruminants, by special characteristics of the uterine mucosa. They differ from the cotyledonary burrs, however, in being proliferations of the surface epithelium. Before the fertilised ova reach the uterus, there are variations in thickness in the mucosa. It is thin at the mesometrial and anti-mesometrial sections, but thickened over the sides to form two cushions, in which the blood-vessels are more numerous. No glands are present near the mesometrium. They are collected on the opposite surface and open into a longitudinal anti-mesometrial groove (Fig. 141).

When the blastocysts reach the uterus, further changes take place. Both the lateral regions increase in thickness by the proliferation of connective tissue cells and the formation of new vessels, while the anti-mesometrial part is widened out into a concave bell-shaped surface into which the glands open. Then the epithelium proliferates, first in the lateral cushions and later in the concave area. In the former the proliferation reaches a thickness of twelve to eighteen cells, and the new elements pass in among the cells and vessels of the deeper layers. In the allantoidean region, the bell-shaped area, the proliferation also leads to a thick epithelial layer with vascular channels between the cells. At intervals, however, the cells are arranged radially like a fan, and later the internal parts of the cells break away and leave a crypt. No crypts are formed in the lateral cushions (Fig. 142).

Over the special areas of the mucosa the trophoblast thickens. It comes in contact first with the lateral cushions by a zonary strip against which the vessels of the area vasculosa spread out. The cell-outlines in the epithelium of the cushions are lost, and a symplasma is formed. At the same time the trophoblast becomes syncytial, is fused to the uterine symplasma, and absorbs part of it. Some of the intercellular channels are opened, and the maternal blood thus begins to circulate in the syncytial lacunæ. At the same time a deeper cell layer, corresponding to the cytoblast of the bat, appears in the trophoblast, but it is never so well marked as in the allantoidean region. In this way the avillous yolk-sac placenta is formed (see also p. 424), and it functions for a time. Soon retrogressive changes appear, resulting in the absorption of the omphaloidean syncytium and epithelium thickenings (Fig. 143). The disappearance is apparently brought about by a newly formed annular proliferation of the trophoblast above the non-placental part, and the degenerated products of the thickened uterine epithelium and of a blood extravasate, which constantly exists between the annulus and the epithelium, are absorbed and transmitted through the hypoblast to the yolk-sac. From it the vessels of the area vasculosa, which at this time reach their full development, carry the nutriment to the developing embryo.

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[1] Hubrecht, "The Placentation of the Shrew," *Quar. Jour. Micr. Science*, vol. xxxv., 1894.

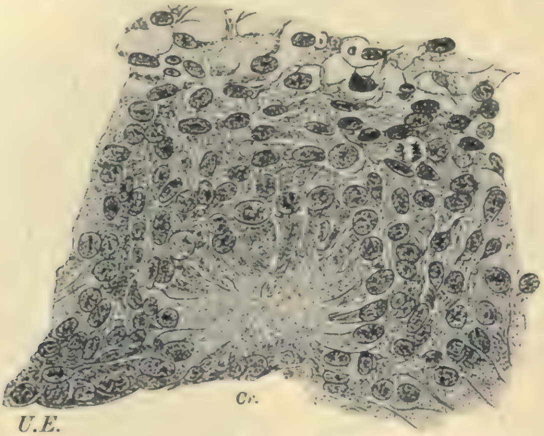

Fig. 142.—Part of the anti-mesometrial wall of the uterus of *Sorex* (Hubrecht). The proliferated epithelium is arranged in a radial fashion, and later it forms a secondary crypt (*Cr.*), when the uterine epithelium (*U.E.*) gives way over it.

The allantoidean trophoblast is applied against the bell-shaped proliferation on the anti-mesometrial side of the uterus, and is fixed by projections which sink into the newly formed crypts. After destroying their epithelial lining, the projections erode capillaries, and the maternal blood circulates in the syncytial lacunæ as in the omphaloidean trophoblast. The cytoblast follows the plasmodial projections, and later the trophoblastic villi are vascularised by the allantoic vessels. Subsequently the plasmodiblast thickens to a considerable extent, and in it the mesoblastic villi continue to branch and form secondary and tertiary villi. There is no penetration on their part into the decidual tissue between the crypts, but the maternal part of the placenta as a whole is gradually absorbed by the plasmodiblast, and is replaced by fœtal elements. In the ripe placenta the only maternal constituent is blood, except a thin discoid sheet of nuclear remnants next the muscularis. The glands are not penetrated by vascular villi. In the early stages they are plugged by syncytium and later disappear.

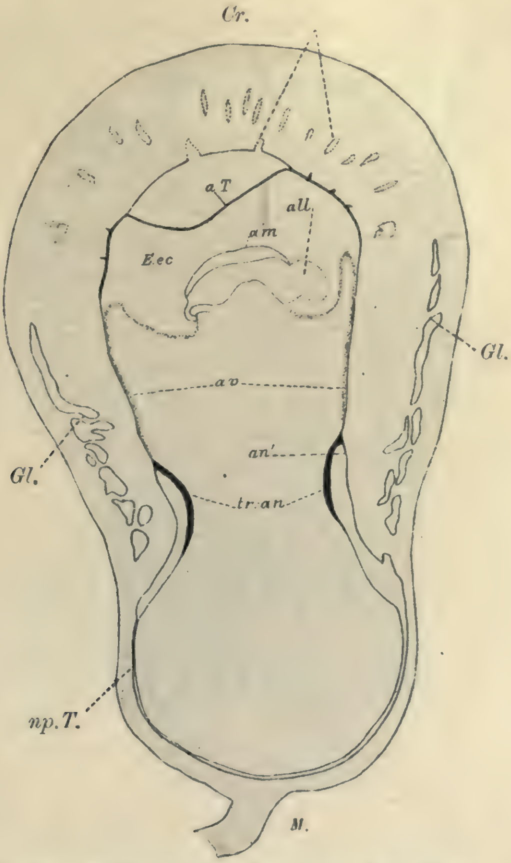

Fig. 143.—Uterus and embryo of *Sorex* (Hubrecht).

a.T., Allantoidean trophoblast with knobs entering the epithelial crypts (*Cr.*); *am.*, amnion; *all.*, free knob projecting into the extra-embryonic cœlom (*E.ec.*); *a.v.*, area vasculosa; *an'*, embryonic cells which grow downwards from the upper rim of the trophoblastic annulus (*tr.an.*), and adhere against the maternal tissue; *np.T.*, non-placental trophoblast; *Gl.*, glands; *M.*, mesometrium.

Mole.—The method of embedding is centric. A simple yolk-sac placenta exists for a time. The allantoic placenta is discoid and is placed anti-mesometrially. The glandular secretion is of importance for the nourishment of the developing fœtus during the greater part of pregnancy (Strahl,[1] Vernhout[2]).

At the beginning of pregnancy the mucosa shows variations in its different parts. Near the mesometrium, for about one-third of the circumference of the lumen, the glandular layer is thin. Anti-mesometrially the muscular layer is not so well developed, but superficially to the glands there is a proliferation of connective tissue cells, through which the ducts run to open into the lumen. The first attachment is in this region.

The uterine horns show a series of small swellings where the ova are present. The blastocysts grow to a comparatively large size, and completely fill up the lumen. By their further growth, the epithelium near the mesometrium is flattened and replaced by trophoblastic cells, which do not penetrate into the connective tissue or form villi. Hence the yolk-sac placenta is of a simple type; it persists throughout pregnancy.

On the opposite side the decidual formation proceeds, and the mucosa becomes thicker. In its substance a rich network of blood-capillaries is developed. The epithelial cells lose their boundaries and form a symplasma. According to Strahl this remains, and forms the syncytial covering of the future villi, but Vernhout has shown that the trophoblast proliferates and forms a layer of epithelioid cells which penetrate into the epithelium and absorb and gradually replace it. Over each gland opening the trophoblast forms a dome as in Ruminants (Fig. 144). In the placental region the glandular epithelium is not changed, and around each opening a small area of the surrounding uterine epithelium persists. In the cavity between a gland orifice and its trophoblastic cap lies a dark secretion, pigmented by admixture with extravasated blood, and the cap is similarly pigmented. Hence the secretion is probably absorbed by the fœtal ectoderm throughout the greater part of pregnancy during which the glands remain. After the disappearance of the surface epithelium at the point of connection with the blastocyst, the plasmodiblast penetrates into the connective tissue layer which forms a symplasma. It is followed by the cytoblast and the allantoic villi. In the syncytium the circulating maternal blood provides for the exchange of gases, and supplements the nutriment supplied by the glandular secretion.

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[1] Strahl, "Ueber den Bau der Placenta von *Talpa europea*," *Anat. Anz.*, vol. v., 1890.

[2] Vernhout, "Ueber die Placenta des Maulwurfs," *Anat. Hefte*, vol. v., 1894.

Tupaia.—In *Tupaia javanica* also the placentation is modified by the characteristics of the uterine mucosa. Hubrecht[1] has shown that two specialised areas, the "Haftflecke," exist before the attachment of the trophoblast. They lie one on each side, about midway between the mesometrial and anti-mesometrial regions, and are recognised by the absence of glandular ducts. The deeper parts of the glands persist till the end of pregnancy, but none open on the modified areas.

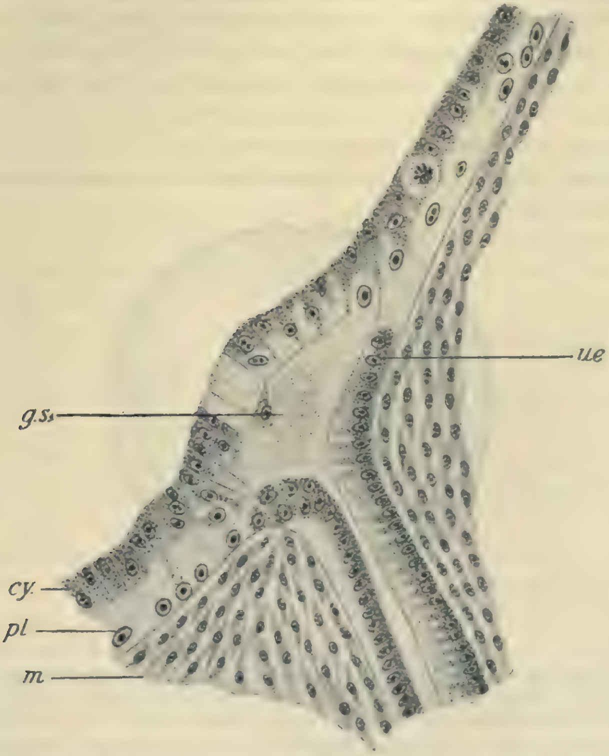

FIG. 144.—Orifice of a uterine gland of the mole with trophoblastic dome. (From Vernhout's "Ueber die Placenta des Maulwurfs," *Anat. Hefte*, vol. v., 1894.)

m., Uterine mucous membrane; *ue.*, uterine epithelium; *pl.*, plasmodiblast; *cy.*, cytoblast; *g.s.*, gland secretion.

The uterine epithelium again disappears at the points of contact with the blastocyst over the "Haftflecke." There the trophoblast becomes thickened, and its cells enlarge and penetrate between the epithelial cells, which fuse to form a symplasma. This is quickly absorbed by the trophoblast, which continues to thicken, and now shows two layers, plasmodiblast and cytoblast. The outer relay fuses so closely with the decidual tissue as to be indistinguishable from it. The capillaries dilate and new vessels are formed, especially in the layers next the ovum. When their endothelium is destroyed, maternal blood enters the trophoblastic lacunæ and soon circulates through them. The inter-vascular connective tissue cells proliferate and form the trophospongia. The decidual layers outside it become fibrillar, and soon are extremely attenuated. The trophospongia remains longer, but finally it also thins, and at the end of pregnancy there is only a thin rim of maternal tissue left.

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[1] Hubrecht, "Ueber die Entwicklung der Placenta von *Tarsius* und *Tupaja*," *Internat. Congr. of Zool.*, Cambridge, 1898.

Over the "Haftflecke" the trophoblast is first vascularised by the vitelline vessels, and a temporary yolk-sac placenta is formed. Later the allantois displaces the yolk-sac, and its vessels vascularise the same part of the trophoblast (Fig. 145). "The permanent placenta replaces the omphalic placenta both physiologically and topographically" (Hubrecht). In this respect *Tupaia* differs from the hedgehog and the shrew.

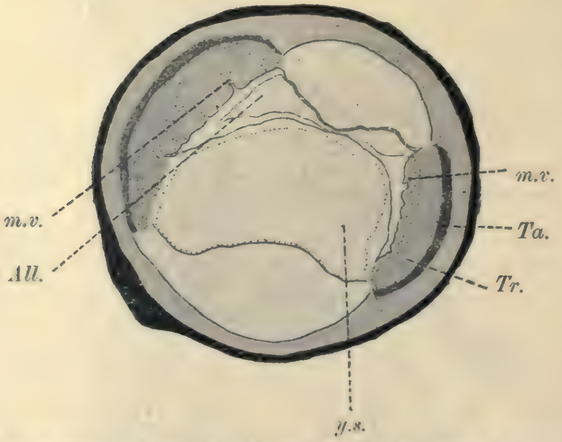

FIG. 145.—Replacement of omphaloidean by allantoidean placenta in *Tupaia*. (From Hubrecht's "Ueber die Entwicklung der Placenta von *Tarsius* und *Tupaja*," *Internat. Congr. of Zool.*, Cambridge, 1898.)

m.v., Mesodermic villi; *Tr.*, trophoblast; *Ta.*, trophospongia; *All.*, allantois; *y.s.*, yolk-sac.

Centetes.—A peculiar form of placentation has been described by Strahl[1] in the tenrec (*Centetes ecaudatus*). A large effusion of maternal blood destroys the centre of the allantoic placenta, and leaves only a peripheral ring. Round the margin of the ring runs a deep groove which is crossed by branches of the allantoic vessels to reach an epithelial ridge of cells.

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[1] Strahl, "Beiträge zur vergleichenden Anatomie der Placenta," *Abh. Senckenberg. Naturf.-Ges.*, 1905. See also Rolleston, "On the Placental Structures of the Tenrec (*Centetes ecaudatus*), etc.," *Trans. Zool. Soc.*, London, vol. v., 1863.

CHEIROPTERA.—The mode of embedding in the bat is centric, and the allantoic placenta is discoid. Before segmentation is completed, the fertilised ovum reaches the uterus and invariably enters the right cornu (Ercolani[1]). The zona pellucida is already thinned and soon disappears, the spherical blastodermic vesicle lying free in the uterine cavity.

At the beginning of gestation, according to van Beneden,[2] the mucosa is composed of a richly cellular connective tissue, covered by a non-ciliated epithelium. Of the glands some are simple tubes, and others divide dichotomously. None open on the mesometrial aspect where the blastocyst later becomes fixed. There also the cellular tissue is not so thick.

Before fixation of the blastocyst, important changes occur in the mucosa. The sub-epithelial connective tissue cells proliferate and form a distinct *compact zone*. All the capillaries dilate, even before the disappearance of the zona pellucida, and give off many new branches. The tissue fluids are increased, and a serous fluid is transuded and forms, with the glandular secretion, a coagulum around the ovum (Van der Stricht[3]).

On the mesometrial side, the trophoblast thickens around the formative cell mass, and absorbs the surface epithelium. At the opposite pole the cells are flattened, and they also disappear. The fœtal ectoderm, which thus comes in contact with the connective tissue, is composed of two layers at the embryonic pole, the *plasmodiblast*, and, internally to it, the *cytoblast*. At the non-embryonic or anti-mesometrial pole the plasmodiblast is absent.

The decidua also differs at the two poles. Opposite the non-embryonic pole the cells remain epithelioid and undergo little change. Where they come in contact with the trophoblast, they show a tendency to necrose. At the placental pole the deeper layers are also composed of epithelioid cells, but superficially the capillaries continue to dilate and make the layer spongy. The cells between them are in active division, but next the plasmodiblast they degenerate. This layer forms the *couche paraplacentaire* of Nolf[4] (Fig. 146). At the placental margin it thins out and disappears.

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[1] Ercolani, "Nuove ricerche sulla placenta nei pesci cartilaginosi e nei mammiferi," *Mem. dell' Accad. d. Sc. dell' Institut. di Bologna*, vol. x., 1879.

[2] V. Beneden, "De la formation et de la constitution du placenta chez le murin," *Comp. Rend. de la Soc. de Biol.*, vol. v., 1888.

[3] Van der Stricht, "La fixation de l'œuf du chauve-souris à l'intérieur de l'utérus," *Verh. d. anat. Gesell.*, 13 Vers., Tübingen, 1899.

[4] Nolf, "Étude des modifications de la muqueuse utérine pendant la gestation chez le murin," *Arch. de Biol.*, vol. xiv., 1896.

Beneath the epithelioid layer in both areas the cells are drawn out and pseudo-fibrous. The conditions for nutrition resemble those in the very early human ovum, the trophoblast lying against a non-vascular detritus-zone. But in the bat there is strong evidence of phagocytosis. The epiblastic protoplasm, where it is in contact with dead tissue, is "crammed with irregular granules, some fatty and others coloured brown with safranin" (Nolf). The mouths of the glands opening at the non-embryonic pole are filled with débris, and their epithelium is degenerated and desquamated. As previously mentioned, no gland-ducts are present in the *couche paraplacentaire*. The blind ends of the glands are, however, distended with secretion, and their epithelium is normal.

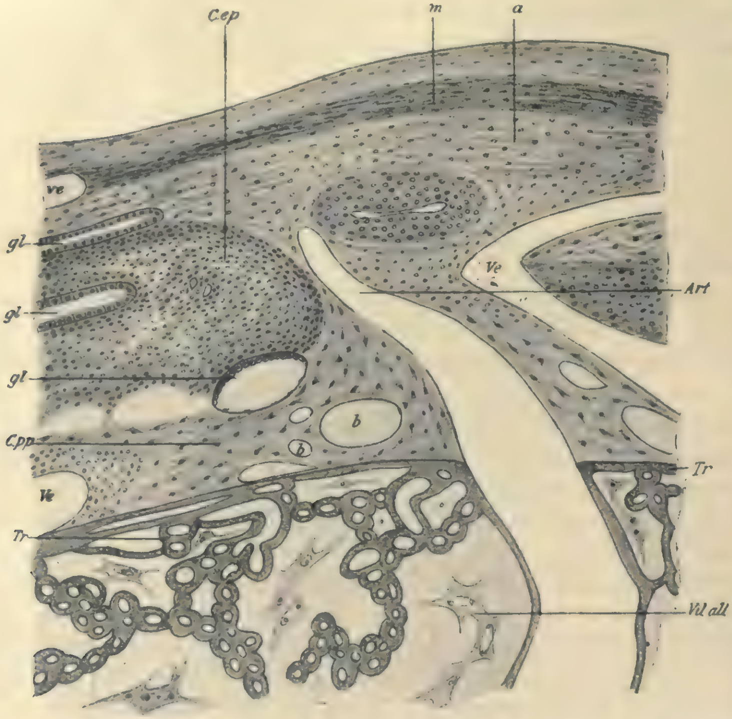

Fig. 146.—The placenta of the bat. (From Nolf's "Étude des modifications de la muqueuse utérine pendant la gestation chez le murin," *Arch. de Biol.*, vol. xiv., 1896.)

m., Muscularis; *a.*, unaltered mucosa; *C.ep.*, epithelial layer; *gl.*, glands; *C.pp.*, paraplacental layer with blood-spaces (*b*); *Art.*, artery running towards trophoblast; *Ve.*, vein; *Tr.*, trophoblast with lacunæ; *Vil. all.*, allantoic villi.

Next a change occurs such as Hubrecht described in the hedgehog (see p. 478). The endothelium of some of the vessels in the paraplacental layer proliferates irregularly round the lumen, and degenerates. In the bat, according to Nolf, the vessels in which the change occurs are the *venous* capillaries, in which the blood, returning from the placenta charged with fœtal excretory products, stagnates and produces the hyperplasia and simultaneous degeneration. Hubrecht, however, states that an endothelial proliferation occurs in arterial and venous capillaries alike in the hedgehog.

At the embryonic pole the plasmodiblast undergoes a marked thickening. It gradually replaces the superficial decidual cells, and surrounds the vessels as in the rabbit. Then it attacks the endothelial sheath and replaces it, so that lacunæ of maternal blood come to be surrounded by fœtal tissue. At the same time the cytoblast sends out cellular buds, which project into the plasmodial mass. Under the cytoblast is the double layer of mesoblast, the thin somatopleur, and the splanchnopleur in which the area vasculosa is developed. A yolk-sac placenta is thus formed in the same region as is subsequently occupied by the allantoic placenta. Nutritive exchanges between maternal and fœtal blood are now possible.

In the further development of the placenta there is very little or no penetration of maternal tissue by the trophoblast (Duval[1]). Degenerative changes occur in the cells of the epithelioid layer in the placental hemisphere. They lose their outlines, and form a symplasma which is absorbed by the adjacent cells of the *couche paraplacentaire* (Nolf). Superficially the paraplacental layer remains until the end of pregnancy. The blind ends of the glands are still distended, but their epithelium degenerates and is cast off into the lumen.

In the non-placental trophoblast, retrogressive changes also occur. Its cells lose their phagocytic power and contain no granules. In the placental area, as already mentioned, the allantois replaces the yolk-sac. The "villi" resemble the tubes of the rabbit. They form a series of arches whose meshes are occupied by allantoic vessels; there are no villi hanging free. As the placenta develops, the thickness of the arches surrounding maternal blood is reduced, and the two blood-streams lie close together. The cytoblast almost entirely disappears.

Pteropus edulis.—In *Pteropus* the placenta is attached to a large mushroom-shaped outgrowth of the uterine wall which grows nearly round the ovum to form a decidua capsularis. As pregnancy advances, the outer wall of the bell-shaped decidual mass is pressed against the uterine surface and fuses with it. In this way the completed placenta is discoid (Göhre[1]).

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[1] Duval, "Étude sur l'embryologie des Cheiroptères," *Jour. de l'Anat. et de la Phys.*, 1895-97.

PRIMATES.—The order of the Primates includes monkeys, apes, and man. Hubrecht and Jenkinson also include *Tarsius*, a lemur (see p. 440). Owing to the difficulties of securing material for investigation, many details regarding the early stages of development of the fœtal membranes and placenta are yet unknown.

From the researches of Turner, it is known that the placentation is in general the same throughout the order, except for differences in the size and form of the villi, and in the structure of the decidua. On the other hand, the Primates are distinguished from all other placental Mammals in that they do not form an allantoic placenta. Notwithstanding the variations in the degree of its development, in all the orders previously considered the allantois projected free into the extra-embryonic cœlom before it was united with the wall of the blastodermic vesicle. In the Primates and *Tarsius* the embryo is attached from the beginning to the wall of the blastocyst by the "Bauchstiel" or "Haftstiel," a mesodermal connecting-stalk first observed by His[2] in human embryos. The allantois appears very early as a recess of the posterior wall of the yolk-sac before the formation of the hind-gut. It never projects free into the cœlom, but is contained as a narrow tube in the "Bauchstiel" without reaching at any time the wall of the blastocyst (Fig. 147). The trophoblast is in this way vascularised directly, and a *chorionic* instead of an allantoic placenta is formed. For this reason Hubrecht has suggested that the term *chorion* should be restricted to the Primates. Minot[3] strongly supported the views of His. He went even further, and stated that the placenta was also chorionic in Carnivora, Rodentia, Insectivora, and Cheiroptera, but his views have not been generally accepted. Regarding the modification in Primates,

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[1] Göhre, "Dottersack und Placenta des Kalong (*Pteropus edulis*)," *Studien über Entwicklungsgeschichte der Thiere*, Selenka, vol. v., 1892. The formation of the amnion in bats has recently been investigated by Da Costa ("Sur la formation de l'amnios chez les Chéiroptères (*Miniopterus schreibersii*) et, en général, chez les Mammifères," *Mem. Soc. Portuguise des Sci. Nat.*, Porto, 1920). He describes three phases: (1) The appearance of a closed cavity in the embryonic disc, the upper wall of which is the primordial amnion; (2) the rupture of this wall and the disappearance of the primordial amniotic cavity, which is replaced by a tropho-ectoblastic space; (3) the formation of an amnion and a definitive amniotic cavity with ectoblastic folds. In some other bats, *Murinus* and the Noctule, it is the same, except that the primordial amniotic cavity is less definite. Primordial amniogenesis of the same type is seen in the guinea-pig, *Galeopithecus Tatusia*, and in Primates. The primitive cavity disappears and is replaced by a cavity which is limited by the amniotic folds in Microcheiroptera, the pig, mouse, etc. The primitive cavity may be absent or only hinted at, as in the hedgehog, mole, rabbit, etc., *Tarsius*, Carnivora (see above, p. 412).

[2] His, *Anatomie menschlicher Embryonen*, I.

[3] Minot, *Human Embryology*, Boston, 1892.

Hubrecht[1] says: "Once the embryonic circulation has found the shortest route towards the trophoblast by way of the 'ventral stalk,' trophoblastic lacunæ, with their profusion of maternal blood, which have been there from the very earliest periods of development, are exquisitely situated for rendering this new adaptation highly advantageous. And while in the ancestral forms of the Primates both yolk-sac and allantois largely drew upon the trophoblastic source, these embryonic organs come to be dispensed with to a very great extent in their more highly developed descendants who come to use that trophoblastic source along a more direct, a shorter, and an earlier established route."

In old-world monkeys there is no decidua capsularis. The trophoblast thickens over two discoid areas on the blastocyst, and the thickenings form a primary placenta on the dorsal surface, and a smaller secondary placenta on the opposite aspect. Hence two groups of chorionic villi are developed.

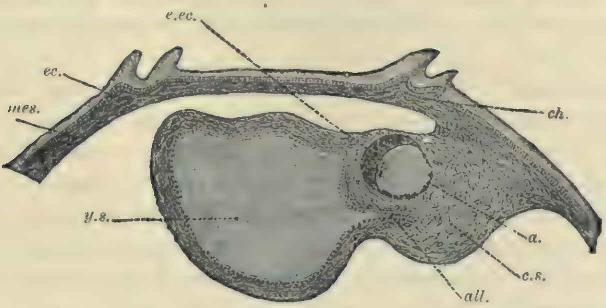

Fig. 147.—Median longitudinal section of an early human ovum, 0·4 mm. in length. (From *Quain's Anatomy*, Longmans.)

e.ec., Embryonic ectoderm ; *ch.*, chorion ; *ec.*, ectoderm ; *mes.*, mesoderm ; *all.*, allantois ; *c.s.*, connecting stalk ; *a.*, amnion ; *y.s.*, yolk-sac.

No unattached blastocyst has yet been obtained. In the youngest specimen of an old-world monkey, *Semnopithecus nasicus*, the ovum was attached to the surface of the uterus by large villous processes with mesoblastic cores at the bases. The trophoblast consisted of two layers, the cytoblast, which was much thickened at the tips of the mesoblastic cores, and, externally to it, a syncytium which was blended at the apices with maternal decidua. Over the non-villous chorion syncytium was absent (Selenka). Spaces, which are in direct communication with maternal capillaries, are present in the syncytium. The most notable characteristic in the decidua is the presence of a glandular secretion in the embryotrophe. In the non-placental area the glands are dilated and open into the uterine cavity, many of them close to the peripheral villi. Hence their secretion may reach the trophoblastic lacunæ. In the placental region they are also dilated, but their superficial parts are closed and appear to degenerate early. In the decidua lie nests of epithelioid cells, the origin of which is uncertain.

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[1] See Robinson's Hunterian Lectures, *Journ. of Anat. and Phys.*, vol. xxxviii., 1904.

The new-world monkeys, like the old-world, have no decidua capsularis, and the placenta is formed as a single disc. In the anthropoid apes, on the other hand, the ovum is lodged in an implantation cavity, and so is covered by a reflexa. The whole circumference of the trophoblast thickens and develops villi, but later they disappear except over a discoid area, the decidua serotina. In the earlier stages two main groups of villi are present as in the old-world monkeys, while the rest of the chorion is covered with smaller villi.

In Selenka's youngest specimen, the ovum was completely enclosed by decidual tissue, and there was no evidence to show whether the mode of embedding was excentric or interstitial. The surface of the ovum was separated from the decidua by a series of intercommunicating spaces, the intervillous spaces, which contained lymph. In other words, Selenka looks on the intervillous space in apes as a space lying between maternal and fœtal tissues, in which villi are suspended.

In man also the villi are at first diffuse, and later restricted to a discoid area, the placenta being again developed in the decidua serotina.

The ovum probably reaches the uterus still enclosed in the zona pellucida, and lies free until the end of the first week, but this stage has never been observed. The uterine mucosa, as in other orders, is matured about the time of puberty (Björkenheim[1]), and then consists of embryonic connective tissue cells, separated from the surface epithelium by a layer of flattened cells. The intercellular spaces are filled with lymph, and they drain into lymphatic vessels in the outer half of the mucosa, where also the arterioles and venules lie. All the blood-vessels in the inner half are capillaries. In all probability the fertilised ovum, during its sojourn in the Fallopian tube and while it lies free in the uterine cavity, does not influence the structure of the mucosa, and may implant itself at any period during the œstrous cycle (Bryce and Teacher[2]). But under the abnormal conditions in a tubal pregnancy, the uterine mucosa undergoes a decidual change although no fertilised ovum is embedded in it.

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[1] Björkenheim, "Zur Kenntnis der Schleimhaut im Uterovaginalkanal des Weibes in den verschiedenen Altersperioden," *Anat. Hefte*, H. cv., 1907.

[2] Bryce and Teacher, *The Early Imbedding and Development of the Human Ovum*, Glasgow, 1908.

In all the early specimens the ovum was completely enclosed in the uterine mucosa, and the actual process of embedding has not yet been observed. John Hunter considered that the ovum reached the uterus from the Fallopian tube under the mucous membrane, and so had a decidua reflexa, while at a *later* stage the mucosa developed underneath it; hence the term decidua *serotina*. Sharpey supposed that the enclosure was effected by *circumvallation*, *i.e.* by a growth round the ovum of two folds of mucosal tissue, which fused and formed the decidua capsularis. But v. Spee[1] discovered a different mode of embedding in the guinea-pig, and later stated that it was the same in man, viz. a destruction of the superficial epithelium, and the implantation of the ovum in the cellular substance of the mucous membrane. This view has received considerable support from the researches of v. Heukelom,[2] Peters,[3] Bryce and Teacher, and others. At the same time it must be borne in mind that His,[4] in describing an early human ovum in 1897, stated that the implantation cavity was lined with epithelium,[5] and thus represented a part of the uterine lumen shut off by the growth of decidual folds.

At the time of embedding, segmentation has probably finished and the ovum is in the condition of the early blastocyst. Its epiblastic wall disintegrates the epithelium, the subjacent cells, and a few capillaries at the point of contact. Hence the blastocyst comes to lie in the connective tissue of the mucosa, which completely surrounds it, except at the point of entrance of the ovum. Here there is a gap in the tissue, the "Gewebspilz," filled up at first by a blood-clot which afterwards becomes fibrinous (Peters), and later by decidual tissue (Kollmann[6]). In Peters' ovum the gap was four-fifths of a millimetre in diameter, and in Bryce and Teacher's a tenth of a millimetre. The size of the ovum when it becomes embedded is probably, according to the last-named authors, a fifth of a millimetre.

When the hypoblast of the early blastocyst is differentiated, it does not apparently line the wall of the blastocyst, but forms a small vesicle. Very early, even before the appearance of the primitive streak, a marked proliferation of mesoblast occurs (Fig. 148). In the youngest ovum its cells filled the space between the wall of the blastocyst and the small amniotic and hypoblastic vesicles. In the ovum described by Leopold,[1] it was already split by the "Haftstiel" into two parts, which enclosed the cœlom and were continuous with each other (Fig. 149). The outer wall of the blastocyst, the fœtal ectoderm or trophoblast which anchors the ovum in the mucosa, is thickened all round its circumference, and even in the earliest specimen contained vacuoles into some of which maternal blood had penetrated. In this thick spongy layer Bryce and Teacher found no cell-outlines anywhere. Hence the transformation to syncytium is not due, as Peters supposed, to the contact with maternal blood. Under the syncytium is the cellular layer, corresponding to the cytoblast of

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[1] V. Spee, "Neue Beobachtungen über sehr frühe Entwicklungsstufen des menschlichen Eies," *Arch. f. Anat. u. Phys.*, Anat. Abth., 1896.

[2] V. Heukelom, "Ueber die menschliche Placentation," *Arch. f. Anat. u. Phys.*, Anat. Abth., 1898.

[3] Peters, *Ueber die Einbettung des menschlichen Eies*, Leipzig u. Wien, 1899.

[4] His, "Die Umschliessung des menschlichen Frucht während der frühesten Zeit der Schwangerschaft," *Arch. f. Anat. u. Phys.*, Anat. Abth, 1897.

[5] *Cf.* Johnstone, "Contribution to the Study of the Early Human Ovum," *Jour. of Obstetrics and Gynæcology*, (May) 1914.

[6] Kollmann, "Die menschlichen Eier von 6 Millimeter Grösse," *Arch. f. Anat. u. Phys.*, Anat. Abth., 1879.

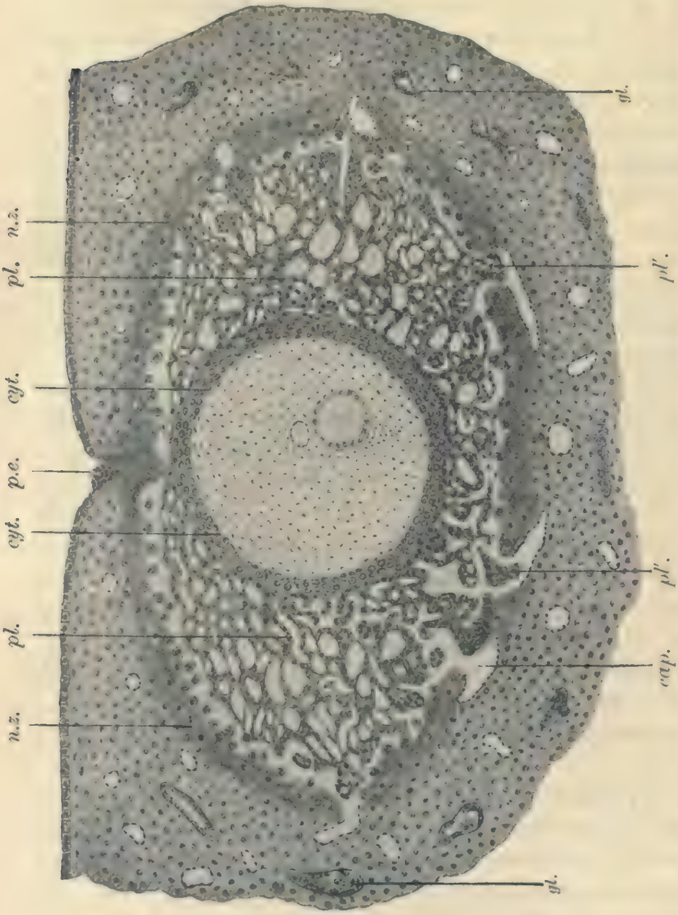

FIG. 148.—Diagram of the earliest human ovum hitherto described. The cavity of the blastocyst is completely filled with mesoblast, and embedded therein are the amnio-embryonic and entodermic vesicles. (From Bryce and Teacher's *Early Development of the Human Ovum*, Maclehose.)

p.e., Point of entrance ; *cyt.*, cyto-trophoblast ; *pl.*, plasmodi-trophoblast ; *n.z.*, necrotic zone of decidua ; *gl.*, gland ; *cap.*, capillary ; *pl'.*, masses of vacuolating plasmodium invading capillaries.

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[1] Leopold, "Demonstration eines sehr jungen menschlichen Eies," *Arbeiten aus d. Königl. Frauenklinik in Dresden*, Leipzig, 1906.

Beneden. Its cells are in a state of active division, and they appear later to lose their outlines and merge into the syncytium. The growth of the latter from the mother-zone of cytoblast occurs, not as a solid mass, but in strands forming primitive syncytial villi (Fig. 150). Into the syncytium project outgrowths of the cytoblast, forming the cellular villi of Peters and Leopold. In the youngest ovum the formation of these buds was just commencing, and, according to Bryce and Teacher, they tended to grow out not so much into the

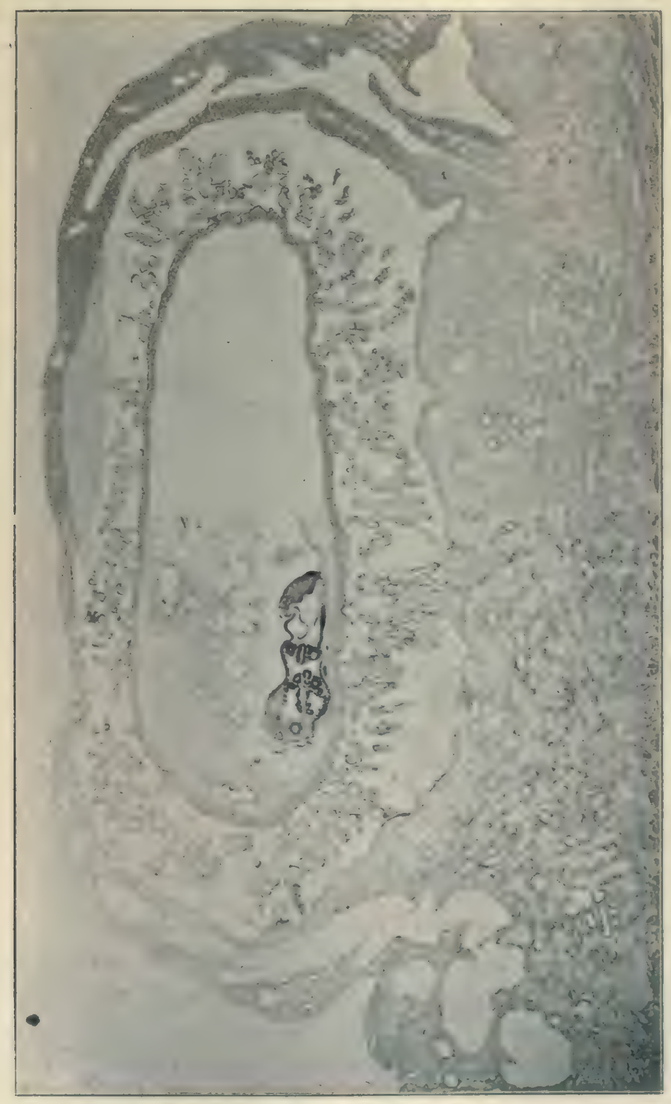

FIG. 149.—Section through the wall of the uterus in the early part of pregnancy (believed by Leopold to be about the fifteenth day). The ovum is shown in relation to the decidua serotina and reflexa (after Leopold). (From Webster's *Human Placentation*, Keener & Co.)

strands of trophoblast as into the spaces between them. Later still, mesoblastic processes penetrate into the cellular buds and complete the vascular chorionic villi.

Round the blastodermic vesicle is a zone of degenerated tissue, the "Detrituszone" (Fig. 151). It is uncertain whether it is formed by the influence of the trophoblast or maternal elements. At its inner edge, and within its spaces, are numerous large mononuclear cells which are "more likely maternal" (Bryce and Teacher). Peters also mentioned the presence of many large cells, and compared them to the deciduofracts of the hedgehog. V. Heukelom described the cellular layer outside the syncytium as fœtal, and derived from Langhans' layer.[1] Whatever their origin, the mononuclear cells in

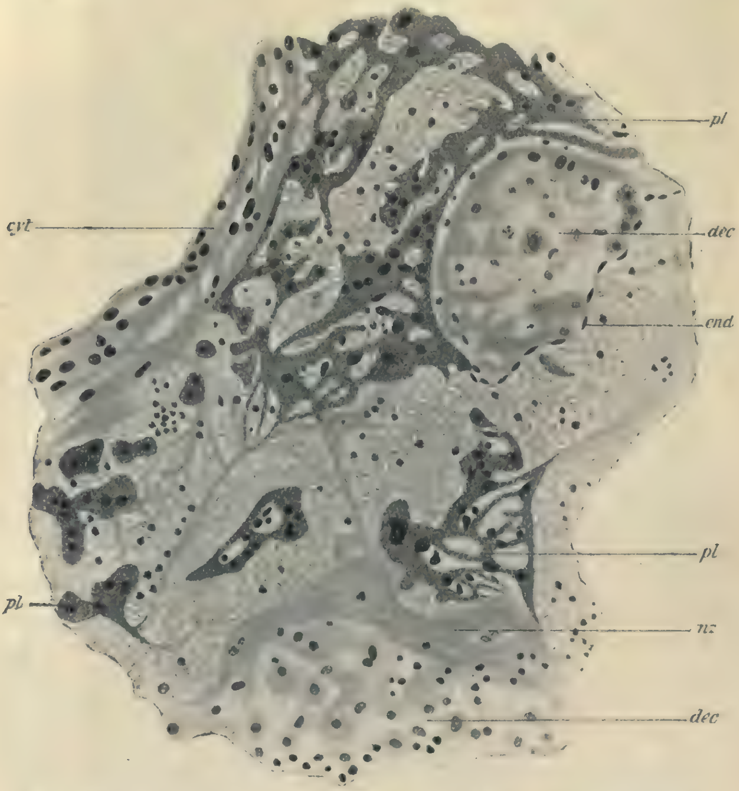

Fig. 150.—Section of a portion of the wall of the human blastocyst. (Bryce and Teacher.)

cyt., Cyto-trophoblast; *dec.*, decidua; *end.*, endothelium of maternal capillary; *pl.*, plasmodium; *nz.*, necrotic zone of decidua.

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[1] Much uncertainty still exists regarding the origin of these large cells in man and other animals. In the mouse, Duval and Sobotta consider them fœtal,

man appear to be engaged in disintegrating mucosal tissue, and producing a zone of coagulation necrosis, *i.e.* a symplasma, around the trophoblast. But they differ from similarly situated cells in lower animals, *e.g.* the mouse, in showing no evidence of ingestion of formed tissue-elements.

In the youngest ova no space exists between the trophoblast and the wall of the implantation cavity (Fig. 152). In later specimens a space is formed, apparently by the absorption of the débris of the necrotic zone. How this excavation is brought about is uncertain. According to Peters, the trophoblast may exercise a phagocytic action. Bryce and Teacher, however, found no evidence of such a process, and inclined to the opinion that the material was dissolved by an enzyme before its absorption. In the trophoblast they found

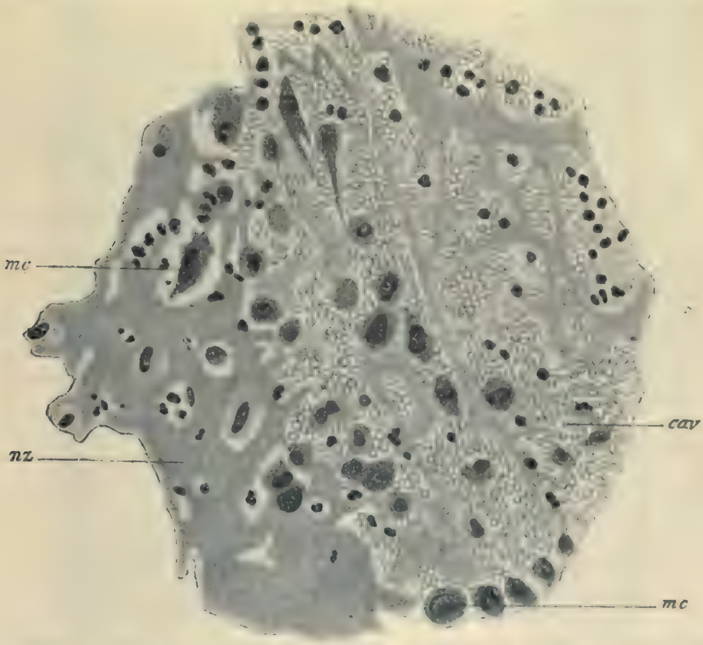

FIG. 151.—Section of a portion of the necrotic zone of the decidua, and of the layer of large cells on its inner aspect. (Bryce and Teacher.)
nz., Necrotic zone ; *mc.*, large cells in various stages of degeneration ; *cav.*, blood-filled implantation cavity.

Kolster and Disse maternal, and Jenkinson both fœtal and maternal. In the guinea-pig, v. Spee states that they are fœtal. In the hedgehog they were first described by Hubrecht as maternal, and later as fœtal. In man, as stated above, the same doubt exists whether the trophoblast consists of two layers, cytoblast and plasmodiblast, or possesses a third layer composed of large cells, and forming the advance guard in attacking the uterine mucous membrane and enlarging the "Eikammer."

that some of the vacuoles were not yet filled with maternal blood, but contained a granular coagulum which might, when liberated, have a digestive activity. In either case, the extensive proliferation of the trophoblast appears to provide for the absorption of the necrosed tissue around it, as well as for the flow of maternal blood into its lacunæ by the erosion of superficial capillaries. These two objects accomplished, the greater part of the trophoblastic proliferation disappears.

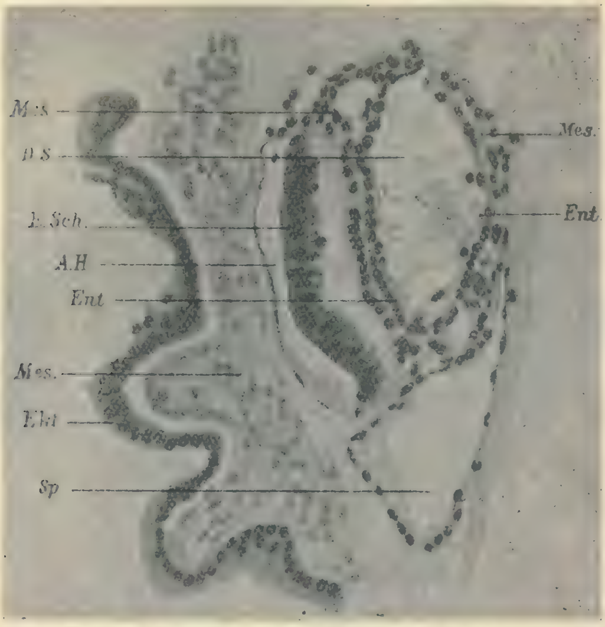

FIG. 152.—Section through embryonic region of ovum (after Peters). (From C. Webster's *Human Placentation.*)

E.Sch., Embryonic epiblast; *Ent.*, embryonic hypoblast; *Mes.*, mesoblast; *D.S.*, umbilical vesicle; *A.H.*, amniotic cavity; *Ekt.*, chorionic epiblast; *Sp.*, space.

Immediately after the excavation of the cavity the decidual formation begins. Before this stage, the changes resemble those that take place during the menstrual period. The vessels are dilated, and blood extravasations occur between the cells and into the lumen. The tissue is œdematous and spongy, and the swollen cells often appear to be floating free in a fluid (v. Heukelom). These changes are especially marked near the ovum, and they give rise to an elevation which marks the resting-place of an early blastocyst. The mucosa is differentiated into a superficial layer, the *compacta*, and a deeper layer, the *spongiosa*, in which are the enlarged middle portions of the glands, arterioles, venules, and lymphatics. In the compacta the connective tissue cells undergo active division, and they enlarge to form the decidual cells (Fig. 153). Before the excavation of the "Eikammer" they are probably not found, though Peters described the commencement of a decidual change before that stage. In Merttens'[1] ovum large decidual cells were found, many of them fusiform and lying parallel to the surface. The decidual change arises first in the connective tissue cells near the ovum, and later it extends more deeply in the compacta. There is no special perivascular development as in the rabbit, and no endothelial proliferation as in the hedgehog and bat, though the latter may occasionally occur in tubal pregnancy (Webster[2]).

The capillaries dilate to sinuses, and new vessels are also formed in the compacta. Many of them are opened by the trophoblast and perhaps by the mononuclear cells, and gradually more and more blood is effused into the trophoblastic lacunæ. In them it does not clot, the syncytium acting as an endothelium, but at a certain stage the blood begins to circulate and continues to do so throughout pregnancy. The gland-ducts are destroyed in the necrotic zone. In the underlying compact zone they are found dilated in the serotina and base of the reflexa, but even in Bryce and Teacher's ovum the epithelium showed signs of degeneration and desquamation.

With the formation of the space between the ovum and the decidua, a permanent attachment of the two structures is brought about. The development of the villi has

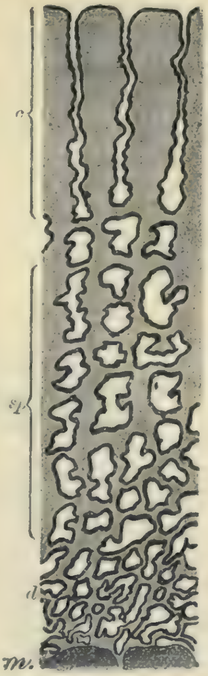

Fig. 153.—Condition of the glands at the beginning of pregnancy in man (after Kundrat and Engelmann). (From *Quain's Anatomy*, Longmans.)

c, Compact layer near free surface of decidua: the glands are here somewhat enlarged, but not very tortuous, and the mucous membrane is rendered compact by the hypertrophy of the interglandular tissue; *sp.*, spongy layer containing the middle portion of the glands greatly enlarged and tortuous, producing a spongy condition in the mucous membrane; *d*, deepest portion of glands, elongated and tortuous, but not much enlarged; *m*, muscularis.

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[1] Merttens, "Beiträge zur normalen und pathologischen Anatomie der menschlichen Placenta," *Zeitsch. f. Geburtsh. u. Gynäk.*, vols. xxx. and xxxi., 1894-95.

[2] Webster, *Human Placentation*, Chicago, 1901. Wade and Watson (*Jour. of Obstet. and Gynec. of Brit. Emp.*, 1908) also state that in tubal pregnancy some of the decidual cells are formed from endothelium.

already been traced up to the stage when they consisted of simple stalks of mesoblast with a double ectodermal covering. In the core are developed capillary vessels which are continuous with the vessels of the "Haftstiel," and later with those of the umbilical cord. After the excavation of the necrotic zone, some of the stalks reach the decidual surface and attach the ovum to it. At first the attached ends of these primary villi are plasmodial, but later the cytoblast proliferates and forms thick rounded masses, the "Zellsäulen," over which the syncytium disappears. This forms the permanent attachment between the villi and the decidual *surface.* The spaces between the stalks form the primary *intervillous space,* which is thus entirely in the plasmodiblast. The primary villi form buds of their three layers which develop into secondary villi. Of these some may also become attached to the decidua, while others hang free in the intervillous space. By a similar process other villi are also developed, till the whole system

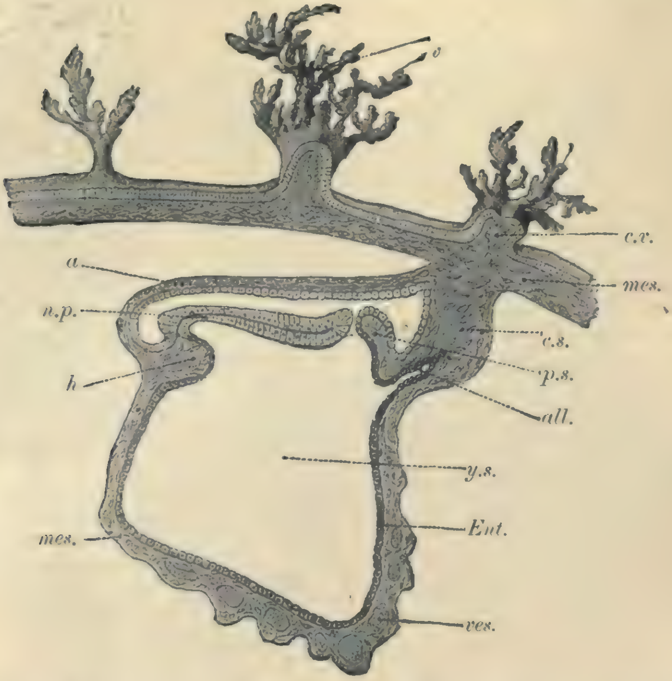

FIG. 154.—Median longitudinal section of an embryo of 2 mm. (von Spee). (From *Quain's Anatomy*, Longmans.)

v., Villus ; *c.v.*, core of villus ; *mes.*, mesoderm ; *c.s.*, connecting stalk ; *p.s.*, primitive streak ; *all.*, allantois ; *y.s.*, yolk-sac ; *Ent.*, entoderm ; *ves.*, vessels ; *h.*, heart ; *n.p.*, notochordal plate ; *a.*, amnion.

becomes branched like a tree (Fig. 154). At first they are equally distributed over the chorion, but the villi in relation to the reflexa do not branch so much, and even at the end of the first month they are fewer in number than over the serotina (Kastschenko[1]). When the blood-supply to the reflexa is reduced, the villi in relation to it degenerate, and are compressed between the chorion and the apposed decidua reflexa and vera. Over the serotina they continue to branch and form the fœtal part of the placenta, which is essentially a mass of fœtal villi between which maternal blood circulates. By the "Haftzotten" the spongy mass is attached to the decidual surface. The attached ends may excavate the decidua to some extent, but there is no great degree of penetration (Fig. 155).

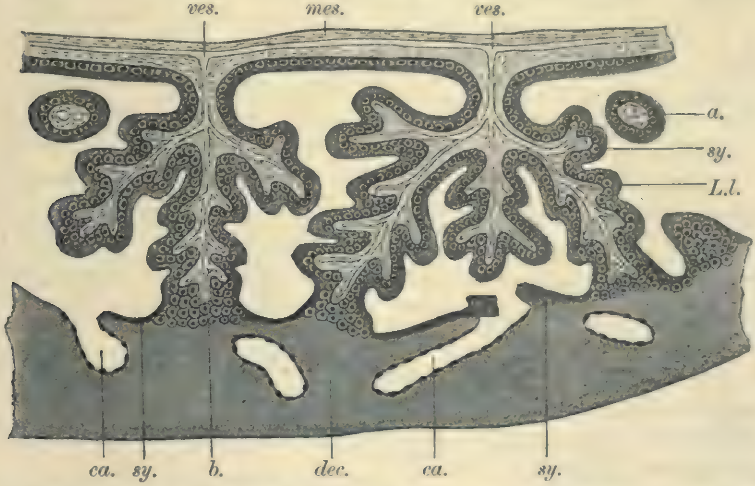

FIG. 155.—Diagram of stage in the development of the human placenta. (T. H. Bryce in *Quain's Anatomy*, Longmans.) The "Haftzotten" are attached to the surface of the decidua. The mesodermic processes are everywhere covered by a single layer of cells (Langhans' layer) and a lamella of syncytium.

b., Attachment of a villus; *mes.*, mesoderm; *ves.*, vessels going to villi; *sy.*, syncytium; *L.l.*, Langhans' layer; *a.*, cross-section of a villus; *dec.*, decidua; *ca.*, maternal capillary.

As pregnancy advances, marked degenerative changes occur in the maternal and fœtal parts of the placenta. The most notable change in the villi is the gradual disappearance of the cytoblast, the mother-zone of the syncytium. Even the "Zellsäulen" tend to disappear from the tips of the villi, and their connective tissue comes in contact with the decidua. Fibrinous changes are frequent in the remnants of the cytoblast and in the mesoblast. The syncytium becomes very thin, and occasionally tracts of it are stripped off.

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[1] Kastschenko, "Das menschliche Chorionepithel und dessen Rolle bei der Histogenese des Placenta," *Arch. f. Anat. u. Phys.*, Anat. Abth., 1885.

The decidua serotina, after reaching its full development during the third month, is gradually thinned out. This may be partly due to the stretching of the tissue by the increasing growth of the uterine contents, but it would seem also to depend on conditions of malnutrition caused by the blood-stasis (Bonnet), and the choking of the lymphatics by the decidual development (Webster). The resulting degeneration takes the form of a coagulation necrosis or symplasma, as shown by the "Fibrinstreifen," which are comparable to the fibrinous deposits in the rabbit's placenta. The layers of fibrin in the serotina were first described by Nitabuch.[1] They may be seen as early as the sixth week, and even earlier in the reflexa (Webster). They gradually extend more deeply into the substance of the decidua, and also occur in the vessel walls. They are, however, most marked on the surface, at or near the junction of the maternal and fœtal tissues. That they are due to the influence of the ovum is highly probable from their absence in the vera. Whether the symplasma is formed from the blood or the decidua, or both, is not known. It is probably absorbed by the villous ectoderm during the greater part of pregnancy.

According to Webster, there may be a new formation of decidual tissue during pregnancy, from irregularly distributed groups of active cells which are present at all periods in the maternal part of the placenta (see p. 402).

The uterine glands take no part in the formation of the placenta. By the sixth week their superficial parts are largely obliterated, and the deeper parts degenerated. At a later stage, only a few blind ends are seen next the muscular layer. Though their epithelium offers a considerable degree of resistance, and is visible for a long time, its secretory power is probably lost very early. According to Gottschalk,[2] the glandular epithelium undergoes a fatty degeneration, but Bonnet[3] states that the change is a hyaline one. In the vera the glands increase in size and secrete actively for a time. Their secretion is found as a milky fluid in the uterine cavity.[4]

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[1] Nitabuch, "Beiträge zur Kenntnis der menschlichen Placenta," *Inaug.-Dissert.*, Bonn, 1887.

[2] Gottschalk, "Weitere Studien über die Entwicklung der menschlichen Placenta," *Arch. f. Gynäk.*, vol. xl., 1891.

[3] Bonnet, "Ueber Syncytien, etc.," *Monatsschr. f. Geburtsh. u. Gynäk.*, vol. xviii., 1903.

[4] Wislocki and Key have studied the distribution and character of mitochondria (which are sometimes regarded as an index of the metabolic activity of a cell) in the mature placenta of man and other animals. It was found that while mitochondria are present in all placental tissues (fœtal and maternal), they are most abundant in the epithelial cells forming the barrier between the two circulations. They are also abundant in the endothelium lining the

Glycogen

Glycogen is present in the early stages of pregnancy. Langhans[1] demonstrated it in the decidual cells, in the cellular proliferations of the trophoblast at the tips of the villi, and in the mesoblast. It was absent in the canalised fibrin and Langhans' layer. Merttens[2] also found it in the decidua near the ovum. Driessen[3] states that it is present in the superficial and glandular epithelium of the uterus in the first month of pregnancy; around the ovum "in cells of doubtful origin" glycogen is plentiful, but absent in the deeper parts of the decidua; in the villi it is not found in the syncytium and Langhans' layer, but is present in the cell-islands at the tips of the villi, and occasionally in the mesoblast. The total amount is, however, much smaller than in Rodents, and represents only about 0·08 per cent. by weight (Cramer[4]).

Fat

Fat was first described in the human placenta by Apfelstedt and Aschoff.[5] They found it during the second month of pregnancy in the syncytium and Langhans' layer, and in the decidual cells near the villi. Eden[6] found fat in the perinuclear protoplasm of the syncytium, and in Langhans' layer and the stroma of the villi. It is also present in the capillary walls (Dastre[7]). The appearances suggested to Eden that "the placenta appears to be a storehouse of nutritive fat just as is the liver." Minute discrete droplets were also present in the decidual cells, and by the sixth month they had increased in number. At full time the serotina still contained fat, but "it is doubtful whether now it is a physiological deposit, as the serotina shows many degenerative changes." At the same time, a fatty degeneration of the decidua is probably pathological and not a constant phenomenon (Klein[8]), and the fat globules in the early

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maternal blood channels and in the glands of the uterine mucosa. (Wislocki and Key, "The Distribution of Mitochondria in the Placenta," *Contributions to Embryology*, vol. xiii., Carnegie Institute (Washington) Publication No. 276, 1921.)

[1] Langhans, "Ueber Glykogen in pathologischen Neubildungen und den menschlichen Eihäuten," *Virchow's Arch.*, vol. cxx., 1890.

[2] Merttens, "Beiträge zur normalen und pathologischen Anatomie der menschlichen Placenta," *Zeitsch. f. Geb. u. Gynäk.*, vols. xxx. and xxxi., 1894-95.

[3] Driessen, "Ueber Glykogen in der Placenta," *Arch. f. Gynäk.*, vol. lxxxii., 1907.

[4] Cramer (A.), "Beiträge zur Kenntnis des Glykogens," *Zeitsch. f. Biol.*, vol. xxiv.

[5] Apfelstedt and Aschoff, "Ueber bösartige Tumoren der Chorionzotten," *Arch. f. Gynäk.*, vol. l., 1896.

[6] Eden, "The Occurrence of Nutritive Fat in the Human Placenta," *Proc. Roy. Soc. London*, vol. lx., 1896.

[7] See Richet's *Dictionnaire de Physiologie*, vol. vi., Article "Fœtus."

[8] Klein, "Entwicklung und Rückbildung der Decidua," *Zeitsch. f. Geburtsh. u. Gynäk.*, vol. xxii.

stages represent an infiltration of fat into the decidual cells from the maternal blood.

From the absence of fat in the more superficial parts of the syncytium, Hofbauer[1] suggests that it may be split up into fatty acids and glycerine before absorption, and then re-synthesised by the fœtal placenta (Fig. 156). Thence it is carried by the blood in a soluble form, and is again deposited in droplets in the heart, liver, lungs, alimentary tract, and spleen of the fœtus. In the later months of pregnancy there is a considerable deposit of fat in the subcutaneous tissue.[2]

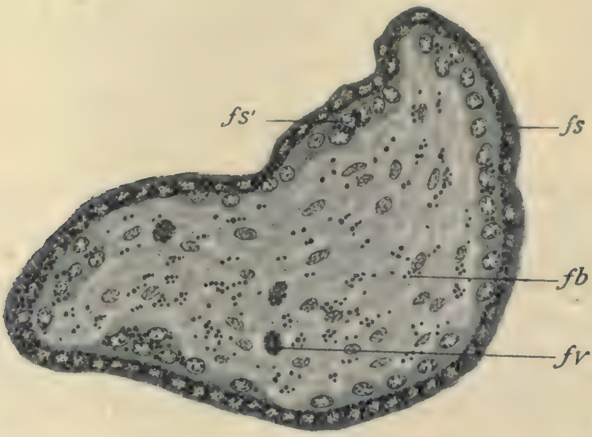

Fig. 156.—Fat in a villus of the human placenta. (From Hofbauer's *Biologie der menschlichen Plazenta*, Braumüller.)

fs., Fat globules in deeper layers of syncytium ; *fs'.*, fat in syncytium between Langhans' cells ; *fb.*, fat in mesoblast ; *fv.*, fat in vacuolated cell.

Lipoids

Bienenfeld[3] states that he found large quantities of lipoids in the placenta in the earlier stages of pregnancy, but that as pregnancy went on the lipoid content decreased. The quantity of lipoids was exceptionally high in the condition of eclampsia.

Respiration

The respiratory exchange in the human fœtus has been studied indirectly by a number of investigators[1] (*cf.* Rodents, p. 464). Hasselbalch[2] found the respiratory quotient of the new-born baby to be unity, thus indicating carbohydrate as the source of the child's energy. Weiss[3] subsequently found the quotient to be between ·7 and ·95. More recently Benedict and Talbot[4] carried out a series of metabolism experiments on 105 newly-born infants, taking special precautions against error. They found that the average respiratory quotient for seventy-four babies during the first twenty-four hours after birth was ·8, thus showing that the substance oxidised could not have consisted entirely of carbohydrate. During the first eight hours, however, the quotient was somewhat higher. It tended to fall until the third day, after which it rose, owing possibly to the carbohydrate supplied in the mother's milk.

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[1] Hofbauer, *Grundzüge einer Biologie der menschlichen Plazenta*, Leipzig, 1905 (see above, pp. 475 and 543).

[2] See also Bondi, "Ueber das Fett in der Placenta," *Arch. f. Gynäk.*, vol. xciii., 1911 ; and Ballerini, "Histochemische Untersuchungen über Fettstoffe und Lipoda im Plazentargewebe," *Arch. f. Gynäk.*, vol. xcviii., 1912.

[3] Bienenfeld, "Beitrag zur Kenntnis des Lipoidgehaltes der Placenta," *Biochem. Zeitsch.*, vol. xliii., 1912. See also Ballerini, *loc. cit.*

Iron

In man, Peters found evidence of the presence of red blood corpuscles in the trophoblast of the early ovum, and Ulesco-Stroganoff[5] states that they are also present in the syncytium in later stages. This has been disputed by Kworostansky[6] and Hofbauer, who maintain that the corpuscles are first dissolved. More recently Bryce and Teacher found no evidence of the ingestion of red blood corpuscles by the trophoblast, while Bonnet[7] has shown that the syncytium gives the eosin-reaction of hæmoglobin at the points where it comes in contact with extravasated blood. It has been stated that placental extracts produce hæmolysis *in vitro* (Veit and Scholten[8]), but whether a similar action takes place in the body is unknown.

Iron-containing compounds are also found in the villi. Using the method of Hall, which demonstrates iron in loose organic compounds, Hofbauer found none such in the superficial layers of the syncytium, but an increasing number of granules were present in the deeper parts. In the mesoblast they again decreased in number, and were altogether absent near the capillary walls (Fig. 157). He suggests that at first the hæmoglobin derivatives are in too firm combination to take on the stain, then they are further broken down and stained granules appear, and later they are again synthesised into non-stainable compounds which reach the fœtal circulation. Such changes were characteristic of the first half of pregnancy. In the second half the iron-reaction of the villi was "extraordinarily slight."

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[1] Feldman, *Principles of Ante-Natal and Post-Natal Child Physiology*, London, 1920.

[2] Hasselbalch, "Respiration Experiments with New-born Infants," originally published in Copenhagen, 1904; republished in English in Benedict and Talbot's memoir, *The Physiology of the New-born Infant*, Carnegie Institute (Washington) Publication No. 233, 1915.

[3] Weiss, "Les Échanges Respiratoires des Nouveaux-nés et l'Indice d'Oxygenation," *Bull. Acad. de Méd.*, Paris, vol. lx., 1908.

[4] Benedict and Talbot, *loc. cit.* This memoir contains other references.

[5] Ulesco-Stroganoff, "Beiträge zur Lehre vom mikroskopischen Bau der Placenta," *Monatsschr. f. Geburtsh. u. Gynäk.*, vol. iii.

[6] Kworostansky, "Ueber Anatomie und Pathologie der Placenta," *Arch. f. Gynäk.*, vol. lxx., 1903.

[7] Bonnet, quoted by Hofbauer, *loc. cit.*

[8] Veit and Scholten, "Synzytiolyse und Hämolyse," *Zeitsch. f. Geburtsh. u. Gynäk.*, vol. xlix., 1903.

Iron is stored in the liver and other fœtal organs. According to Bunge,[1] it diminishes rapidly after birth, and he supposes that it compensates for the insufficient amount of iron contained in the mammary secretion.

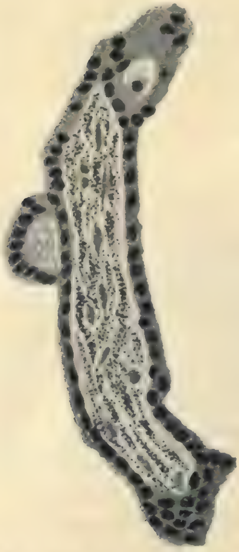

FIG. 157.—Iron granules in a villus of the placenta in man. (From Hofbauer's *Biologie der menschlichen Plazenta*, Braumüller.)

Albumen

The transmission of albumen to the fœtus of the rabbit has already been referred to (see p. 464). In the human placenta attention has been chiefly directed to the investigation of the decomposition products of proteins. Matthes[2] and Hofbauer state that albumoses are present in the placenta, but this is doubtful. In watery extracts Rieländer[3] demonstrated purine bases, uracil and choline, and in the autolysed placenta leucine and tyrosine have been found (Basso[4]). It is generally held that such results prove an active metabolism of protein in the fœtal placenta.

Creatin and Creatinine

Hunter and Campbell[5] have investigated the concentrations of creatin and creatinine in the fœtal and maternal blood. Their method was to take a sample of blood from the placental end of the umbilical cord as soon as it was cut and at the same time from the arm vein of the mother. They found a very slightly higher concentration in the fœtus. They conclude that the placental transmission of creatin and creatinine is a simple process of diffusion.

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[1] Bunge, "Ueber die Aufnahme des Eisens in den Organismus des Säuglings," *Zeitsch. f. phys. Chem.*, vol. xvii., 1893.

[2] Matthes, "Ueber Autolyse der Placenta," *Centralbl. f. Gynäk.*, 1901.

[3] Rieländer, "Ein Beitrag zur Chemie der Placenta," *Centralbl. f. Gynäk.*, 1907.

[4] Basso, "Ueber Autolyse der Placenta," *Arch. f. Gynäk.*, vol. lxxvi.

[5] Hunter (A.) and Campbell, "The Placental Transmission of Creatinine and Creatin," *Jour. of Biol. Chem.*, vol. xxxiv., 1918.

Ferments

Various enzymes have been investigated in the placenta. They may be grouped according to the chemical nature of the actions which they produce, as follows: (1) Hydrolytic reactions, (2) oxidation reactions, (3) removal of amino groups from amino-acids, and (4) decomposition of peroxides.

(1) A proteolytic enzyme was found by Ascoli,[1] and subsequently by Merletti,[2] Bergell and Liepmann,[3] Savarè,[4] and others. Bottazzi[5] states that placental tissue can transform glycogen into maltose, and a similar action is strongly produced by glycerine extracts of the maternal and fœtal placenta of the rabbit (see p. 462).

Savarè holds that the transformation of glycogen to sugar is due to the blood; but the fact that extracts of the Ungulate placentæ, which also contain blood, do not possess the same power, forces us to conclude that the enzyme activity in the rabbit and man depends on the placental tissue. No lipolytic enzyme is present in the placenta (Charrin and Goupil[6]).

(2) The oxidation of aromatic aldehydes by the placenta has been obtained by Hofbauer and by Ferroni,[7] not by Savarè or Charrin and Goupil. V. Fürth and Schneider[8] state that tyrosine is oxidised by contact with the placenta, resulting in the production of a dark pigment, and they have suggested that this reaction may be related to the special pigmentation of pregnancy.

(3) Savarè states that the placenta transforms the NH_2 group of amino-acids into ammonia by means of a special ferment, a desamidase.

(4) Decomposition of peroxides may be produced by enzymes, the so-called indirect oxidases, and is sometimes regarded as the means by which oxidation changes are restricted to the appropriate parts of the body, and secluded, for instance, from the blood (Leathes[9]). The guaiacol reaction, by which a colourless solution of guaiacol becomes red, takes place, according to Charrin and Goupil, when hydrogen peroxide is present; in other words, placental tissue decomposes the peroxide, and the nascent oxygen oxidises guaiacol. Hofbauer,

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[1] Ascoli, "Passiert Eiweiss die placentare Scheidewand?" *Zeitsch. f. phys. Chemie*, vol. xxxvi., 1902.

[2] Merletti, "Ricerche e studi intorno ai poteri selettivi del' epitelio dei villi coriali," *Rass. d'Ost. e. Ginec.*, 1903.

[3] Bergell and Liepmann, "Ueber die in der Placenta enthaltenen Fermente," *Münch. med. Woch.*, 1905.

[4] Savarè, "Zur Kenntnis der Fermente der Placenta," *Hofmeister's Beiträge*, vol. ix., 1907.

[5] Bottazzi, "Placental Activity," *Boll. della R. Accad. med. Genova*, vol. xviii.

[6] Charrin et Goupil, "Physiologie du Placenta," *Compt. Rend. de l'Acad. des Sciences*, vol. cxli., 1905; also vol. cxlii., 1906.

[7] Ferroni, "L'eterolisi utero-placentare," *Ann. di Ost. e Ginec.*, 1905.

[8] V. Fürth and Schneider, "Ueber tierische Tyrosinasen und ihre Beziehungen zur Pigmentbildung," *Hofmeister's Beiträge*, vol. i.

[9] Leathes, *Problems in Animal Metabolism*, London, 1907.

however, says that the presence of hydrogen peroxide is not required, *i.e.* that the placenta acts as a direct oxidase.

No glycolytic ferment is present in the placenta.[1]

A few ferment actions still remain—*e.g.* the removal of urea from arginin, the decomposition of uric acid, and the oxidation of purine bases—which have not yet been investigated in the placenta.[2]

V. General Considerations of Fœtal Nutrition and the Placenta

A. *The Plan of Placental Formation*

The problems of fœtal nutrition are not new problems. They deal with the assimilation of organic and inorganic substances, and their incorporation in the developing tissues. These phenomena are made up of a series of chemical changes which must be studied individually before we can hope to understand the final sum which constitutes fœtal metabolism, or the disturbances which constitute fœtal disease. Set in the path traversed by the materials on their way to the new organism is the placenta, a complex organ composed of specialised maternal elements and newly developed fœtal elements. Among the Monodelphia no uniform plan is observable in the formation of the placenta, nor is it possible to trace each step in its evolution. But Duval's conception of this temporary organ as a maternal hæmorrhage surrounded by fœtal elements, and Hubrecht's discovery of such a type of placenta in a mammalian order which is among the most archaic, lead to a change in the ideas of placental classification. We can no longer depend on the shape of the placenta or the characteristics of the after-birth, for an understanding of its morphological or physiological features. Rather must we go back to the phenomena to be observed in the uterine fixation of the blastocyst, and even earlier in the preparation for that fixation. At this stage we find two constant features, one maternal and the other fœtal. The maternal change consists of an epithelial, connective tissue or endothelial proliferation, the trophospongia, which is "specially intended for the fixation of the blastocyst." According to Hubrecht, it degenerates into a symplasma when the fixation is accomplished and the fœtal elements are in contact with circulating maternal blood. But its degeneration is not completed at that stage. Though individual cells may die, other cells are formed and take their place, at least in man, throughout the greater part of pregnancy. Moreover, the cells have other functions to perform. Whether or not they act as a defence against the excessive penetration of the trophoblast, they continue in the rabbit to exercise the glycogenic function for the developing organism till the hepatic cells have attained the power, and there is reason to believe that they play a part in the iron metabolism of the fœtus.

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[1] It cannot yet be held as proved that glycolysis by ferment action occurs at all in animals.

[2] For a further study of the ferment content of the placenta see above, p. 465.

The embryonic preparation is the proliferation of the whole or part of the extra-embryonic ectoderm, the trophoblast, in the spaces of which maternal blood circulates. The outer layer is plasmodial, and thus resembles the maternal symplasma in histological appearance, but differs from it in being a live tissue while the other is dying or dead. The fusion of the trophoblast and trophospongia constitutes the placenta, which is perfected by an increase in the number and size of the trophoblastic lacunæ, and in the amount of maternal blood in contact with it.

The above description does not, however, fit the placenta of Ungulates, for in them the trophoblast is not permeated by maternal blood. If the Insectivore placenta represents the primitive type, or is nearer to it than any other at present existing, we must assume that the Ungulate placenta, differing more widely from the original type, has lost this characteristic. Further, the placenta of the pig must have undergone a greater degree of modification than that of the sheep. In other words, the old ideas of placental evolution, based on the researches of Turner and others, must be literally reversed. The Primates must stand with the Insectivores near the primitive type, while the sheep and pig are near the opposite end, where some of the Didelphia are placed. Such considerations as these must inevitably come up for discussion in all future investigations.

B. *The Nature of the Trophoblastic Activity*

During the period of gestation, the mother organism is concerned with the provision of material for the growth and development of the fertilised ovum and the new-born young. Does the material provided for the ovum, and secured for it by the trophoblast, come from the maternal tissues or from the food supply? There is no doubt that in insufficient nutrition the fœtus draws on the tissues of the mother (Jägerroos[1]), and a study of comparative placentation goes far to prove that this is a normal process in some orders. It is obvious that such occurs in the earliest stages. In all orders, before fixation of the blastocyst to the uterine mucosa, the degenerating ovarian cells which surround the extruded ovum form a store of nutriment. In some animals, however, such as the opossum, in which no attachment of the blastocyst can be said to occur, and the sheep, in which the attachment is long delayed, this nutriment is added to by the secretion of the uterine glands. In the so-called Deciduate orders, fixation is effected by a phagocytic or chemical action on the part of the trophoblast, and the destroyed maternal tissue again seems to serve as food for the blastocyst.

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[1] Jägerroos, "Der Eiweiss-, Phosphor-, und Salzumsatz während der Gravidität," *Arch. f. Gynäk.*, vol. lxvii.

After fixation, differences appear in the various orders. In Ruminants a special nutritive secretion, the uterine milk, is elaborated in the inter-cotyledonary areas. This secretion contains cellular elements of maternal tissue, particularly leucocytes and glandular epithelium, which are ingested and dissolved by the trophoblast during the whole period of gestation. In addition, extravasations of maternal blood or individual corpuscles occur in all, and the erythrocytes are also taken up and dissolved. In such orders maternal tissue elements are normally used for the fœtus throughout pregnancy.

Among the Deciduata, however, with the exception of the mole, in which the glandular secretion is maintained, the maternal blood may be considered to be the only source of fœtal nutriment when the allantoic or chorionic placenta is developed.[1] In them the trophoblast resembles a sponge saturated with slowly circulating blood, and its large superficies is admirably adapted for the acquisition of the various materials required for the fœtus. In what form do these materials exist in the blood? Are they simply the substances absorbed from the food by way of the intestine (see also Chapter XI., p. 521), or are they more highly elaborated? In other words, in the formation of the new organism are the syntheses carried out by the fertilised ovum itself, and it must be remembered that this includes the trophoblast, or are the new tissue-elements transferred ready-made from the mother? The limitations of biological chemistry force us to approach this problem indirectly. Differential analyses of special constituents of the blood, as the proteins, in the non-pregnant and pregnant animal are not yet possible.

In the first place, a brief consideration of the development of the chick embryo is sufficient to prove the high degree of activity vested in the ovum of birds. The special proteins and other tissue-elements are not pre-formed, but are elaborated by a series of katabolic and anabolic processes which are carried out by the ovum itself. There is no reason to believe that the mammalian ovum, after acquiring the property of intra-uterine development, has lost its metabolic activity.[2]

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[1] The Carnivora, in which the trophoblast is not in contact with *circulating* maternal blood, occupy a special position among the Deciduata, and are not considered above.

[2] If Hubrecht's view is correct, that the mammalian ovum is older than the ovum of birds (see "Early Ontogenetic Phenomena in Mammals," *Quar. Jour. Micr. Science*, 1908), the sentence ought to read: "There is no reason to believe that the fertilised ovum of birds acquired its metabolic activities only after the loss of viviparity."

In addition, we possess positive evidence of metabolic activity in the mammalian ovum. The results of Bohr's investigations on the respiratory exchange of the fœtus (see p. 464) mean nothing if they do not afford proof of this. As a large amount of energy is generated, while, at the same time, practically none is dissipated as heat evaporated or radiated from the surface or lungs, the unavoidable conclusion is that the fœtus itself carries out the work of organisation, and utilises the energy for its fulfilment.

When we come to consider individual substances, we obtain further evidence of activity, at least in the extra-embryonic ectoderm or trophoblast. In no order of Mammals has the transmission of hæmoglobin as such from mother to fœtus been demonstrated. Even if it is absorbed as such by the trophoblast, it undergoes changes of such a nature that the iron-containing part of the molecule is less firmly bound. In all animals in which special investigations have been made, such loose organic compounds of iron have been observed. In this connection, reference may once more be made to Hofbauer's statement that the histological appearances argue not only for a decomposition of maternal hæmoglobin in the syncytium, but also for a synthesis of its derivatives into organic compounds in which the iron is more firmly bound (see p. 505).

The trophoblast probably acts also on simpler proteins. If ox-serum is injected into a pregnant rabbit, its proteins cannot be detected by the biological reaction in the serum of the fœtus. It may be that the trophoblast rejects them altogether, but this is unlikely, since molecules of egg-albumen are absorbed and transferred to the fœtus (see p. 464). In all probability the proteins of ox-serum are katabolised in the villi, and, as a result, the constitution of the precipitable substance is interfered with, and the precipitin reaction is negative. The existence of an intra-cellular proteolytic enzyme[1] and decomposition products of the proteins in the placenta also point to the occurrence of a trophoblastic metabolism of proteins.

The carbohydrates undergo changes which appear to be the result of trophoblastic activity. In the rabbit, the glycogen which is "swallowed" along with the decidual cells by the plasmodium (Chipman) is not found as glycogen. A hydrolytic transformation to sugar probably takes place (see p. 462). In addition the fœtal serum contains lævulose, which must be formed in some part of the fertilised ovum, since it is absent in the mother. Fats may also be transformed by the trophoblast (see Chapter XI., p. 542).

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[1] It is desirable that the presence of the enzyme in the *trophoblast* should be established, and this can only be done in such animals as the sheep and rabbit, in which the fœtal placenta can be detached from the maternal, and investigated separately. As was previously mentioned, the placenta contains no *extra-cellular* proteolytic enzyme.

It is generally supposed that many syntheses occur in the fertilised ovum, though direct evidence is difficult to obtain in Mammals. In the chick hæmoglobin is synthesised, and the same almost certainly occurs in man and other animals, part of the synthesis being effected by the trophoblast (see p. 505). The nucleoproteins of the fœtal cotyledons in the sheep appear to be formed there, since they differ in composition from the nucleoproteins of the cotyledonary burrs. The glycoprotein mucin is a characteristic constituent of the intercellular ground-substance of the whole fœtal organism, and is apparently built up by the ovum.[1] The chondroproteins, a special group of glycoproteins, which yield on hydrolysis proteins and the carbohydrate-containing chondroitin-sulphuric acid, are also found chiefly in the fœtus as constituents of the cartilage and tendons.

A consideration of these and similar facts leads us to believe that the new organism owes its development in large part to the energy generated in it and by it from the combustion of substances supplied by the mother, and to a series of active metabolic changes by means of which these substances are transformed into living protoplasm. Whether the nutritive materials are derived from the food or tissues of the mother is of secondary importance. What is essential is that the fertilised ovum obtains certain organic and inorganic compounds and a supply of oxygen to carry out its work of organisation, just as in the first period of extra-uterine life the growth and development of the new being progress by its own activities, so long as it is furnished with the proper materials.

The special organ of embryonic nutrition is the trophoblast, and evidences of its katabolic activities have been described in various orders of Mammals. But in addition to procuring fixation of the blastocyst to the uterine mucosa, and absorbing and katabolising the food for itself and the embryonic portion of the ovum, it seems also to possess anabolic functions, at least in the earlier periods of pregnancy. Already developed in the blastocyst stage, it is active and functional for a considerable time. But in the later stages it exhibits in all orders of Mammals a degree of morphological degeneration which is incompatible with the maintenance of its early physiological activity. It is further to be noted that its condition varies inversely with the food requirements of the embryo. When the daily requirements for the new organism are almost infinitesimal, the trophoblast is well developed. But as the daily transmission of nutriment increases, the trophoblast, which is now represented by the ectodermal covering of the villi, gradually and progressively degenerates. At the end of pregnancy the cytoblast, the mother zone of the plasmodiblast, is reduced to a few scattered groups of cells, while the plasmodial layer itself is no thicker than an endothelium, and may be altogether absent over long stretches of the villi. At this stage it is impossible to believe that the syncytium has any vital functions to perform. Indeed, we know that it has none, because the fœtus, if prematurely born, is able to maintain life without its aid. Hence it seems likely that in the later stages the extra-embryonic ectoderm, though allowing a greater amount of material to pass to the fœtus each day, acts merely as a semi-permeable membrane, and has lost all, or nearly all, its physiological activity.[1]

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[1] In the placenta of the cow, Jenkinson has described cells resembling goblet-cells in the lining of the cotyledonary crypts, and ascribes to them a maternal origin (*Proc. Zool. Soc.*, London, vol. i., 1906). They may supply mucin to the uterine milk, and so to the trophoblast. According to Assheton, these lining cells are trophoblastic in the sheep.

What is the difference in the early stages of pregnancy, when the trophoblast is morphologically well-developed? We believe that at that time the extra-embryonic ectoderm has less to do with the quantity, and more with the quality, of the material transferred to the new organism. It does not act merely by the physical laws of diffusion and osmosis. At this stage the cells of the ovum have not yet departed widely from a general type, and the active trophoblast would seem to spare the embryonic cells much of the work of the elaboration of the food materials, and thus conserve their energies for their own multiplication and differentiation. As the cells gradually depart further and in different directions from the original type, each cell requires to expend less energy on its own specialisation; at the same time, the nutritive wants become more varied, and each cell requires to expend more energy on the synthesis of its individual protoplasm. As the duties of selection and anabolism are more and more taken up by the cells themselves, the trophoblast has a less important part to play, and it undergoes a gradual process of degeneration.[2]

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[1] Hofbauer's observations on the hæmoglobin metabolism, already quoted (see p. 505), furnish concrete evidence of such a change in the trophoblast. In the first half of pregnancy the syncytium breaks down the maternal hæmoglobin, and subsequently builds it up in part for the fœtus. But in the second half, though a greater daily supply of organic iron is required for the formation of hæmoglobin and other purposes (see p. 547), the amount of loosely bound iron-compounds in the villi is "extraordinarily small." The only explanation is that the larger molecules of the more firmly combined iron-compounds are not attacked and broken down so strongly by the syncytium, but are passed on to the fœtal circulation.

[2] A similar change occurs in the decidual cells of the rabbit. In the first periods of their existence, they synthesise and store a large quantity of glycogen. In the last week, the cells of the fœtal liver assume their glycogenic function, apparently absorbing the carbohydrate from the fœtal blood as it returns from the placenta, and the decidual cells degenerate with the loss of their function.

CHAPTER XI

THE CHANGES IN THE MATERNAL ORGANISM DURING PREGNANCY[1]

> "We cannot reason with our cells, for they know so much more than we do that they cannot understand us; but though we cannot reason with them, we can find out what they have been most accustomed to, and what therefore they are most likely to expect; we can see that they get this, as far as it is in our power to give it them, and may then generally leave the rest to them."—
> SAMUEL BUTLER.

I. THE STIMULUS FOR THE MATERNAL CHANGES

THE anatomical and physiological changes which occur in the maternal organism during pregnancy are manifold. They affect not only the generative system, but the body in general. They are associated with the supply of nutriment and energy for the formation of a new organism in the uterus, and the preparation for its maintenance in the succeeding period.

What constitutes the original stimulus for the changes that occur in pregnancy remains still outside our ken. At least the influence of the cerebrum is not all-important, as is shown by the occurrence of normal pregnancy and lactation in women suffering from paraplegia (Brachet,[2] Kruieger and Offergeld[3]). Similarly, transection of the spinal cord in the lumbar region has no effect on pregnancy in the dog (Goltz[4]). Further, Goltz and Ewald[5] have proved the absence of any spinal reflex influence in the dog by removing the entire lumbar cord without disturbing the onset and progress of pregnancy. Kruieger and Offergeld state, as the result of numerous experiments, that the central nervous system has no influence, and the sympathetic system has an effect only in so far as it modifies the circulatory conditions. The only change observed, after destruction of the lumbar cord, was a prolongation of the act of parturition, due to an absence of pain and the [illegible] the abdominal muscles. The most impo[illegible] the reflex contractions of the uterus are contained in the uterine, paracervical, and [illegible] for ganglia, but their excitability to external stimuli gradually decreases during pregnancy and is lost at the end.

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[1] By James Lochhead and W. Cramer.

[2] Brachet, *Recherches*, 2nd Edition, Paris, 1837.

[3] Kruieger and Offergeld, "Der Vorgang von Zeugung, Schwangerschaft, etc.," *Arch. f. Gynäk.*, vol. lxxxiii., 1908.

[4] Goltz, "Ueber den Einfluss des Nervensystems auf die Vorgänge während der Schwangerschaft, etc.," *Pflüger's Arch.*, vol. ix., 1874.

[5] Goltz and Ewald, "Der Hund mit verkürztem Rückenmark," *Pflüger's Arch.*, vol. lxiii., 1896.

We are thus forced to conclude that the phenomena of pregnancy and parturition are brought about by chemical stimuli acting through the blood-stream. The hormone or hormones may arise in the corpus luteum, which is essential for the progress of pregnancy, at least in the early stages (Marshall and Jolly[1]). Evidence is also forthcoming that the mammary secretion is due to an ovarian influence in certain cases. For instance, secretion may occur in virgin women who are the subjects of ovarian tumours, and in virgin bitches. Cramer[2] has recorded a case in which the transplantation of ovaries into a woman, whose genital organs were much atrophied, led to a secretion of colostrum.[3] On the other hand, removal of the ovaries at the middle of pregnancy does not interfere with the second half of the period of gestation, or with labour and lactation.

The presence of the placenta may modify the normal metabolism in various ways. It is set in the path traversed by the formative material on its way to the embryo, and by the waste products excreted by the embryo. The form in which the materials required by the product of conception reach the placenta is still obscure. The protein may be merely the "circulating protein" found in the non-pregnant condition, or more highly elaborated. The diffusion of the blood-sugar to the fœtus is disputable,[4] and the form of the fats is unknown. Of the waste products, carbonic acid, which, according to Bohr,[5] results entirely from the combustion of carbohydrates in the mammalian fœtus, is excreted into the maternal circulation through the placenta. With regard to a wastage in the protein metabolism, a certain loss is bound to occur in the transformation of "circulating" or "fixed" maternal proteins into fœtal tissue proteins; and in addition, incompletely oxidised substances may possibly be transmitted to the placenta and oxidised there or in the mother (Bohr[6]). The question of urea formation by the fœtal liver or the trophoblast still awaits investigation. The only observation bearing on this point is that human placenta contains urea, and of Hammett.[1] [illegible] is greatly increased in this organ in toxæmic pregnancies. He also found that urea is formed when the placenta is allowed to undergo autolysis. No proof exists of the excretion of urea otherwise than into the liquor amnii. Nor does its presence in the amniotic fluid necessitate an oxidation of protein; it may be split off, as in the adult, by a simple hydrolytic cleavage. At present we must be content with assuming the possibility of modifications in the maternal blood from the presence of fœtal nutritive and waste materials. Hitherto the investigations have been largely confined to human pregnancies, in which individual differences are at a maximum, and the application of the experimental method is restricted. Hence our knowledge of the chemical changes in the blood is very limited. Its composition may, in addition, be modified by the activities of the placenta itself. Several theories have been put forward in support of the view that this organ acts as an internally secreting gland. Nattan-Larrier[2] goes so far as to state that the secretion can be demonstrated in the form of globules lying on the surface of the villi, but these arise in the *post-mortem* degeneration of the tissue. Of the same nature are the products of the placenta which have a blood-pressure raising action. Extracts of the fresh organ have no pressor effects, nor do they increase uterine contractions.[3] Halban[4] considers that the placenta secretes a hormone which stimulates the growth of the mammary gland and the secretion of milk.[5] Starling[6] suggested, on the other hand, that the hormone was contained in the tissues of the fœtus, that by its activity during pregnancy it led to a proliferation of the mammary tissue, and that the cessation of the stimulus after parturition brought on the secretion of milk.

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[1] Marshall and Jolly, "The Ovary as an Organ of Internal Secretion," *Phil. Trans. Roy. Soc.*, London, B., vol. cxcviii., 1905.

[2] Cramer (H.), "Transplantation menschlicher Ovarien," *Münch. med. Woch.*, 1906.

[3] With regard to the existence of an ovarian stimulus, see also Hildebrandt (*Hofmeister's Beiträge*, vol. v., 1904).

[4] See Chapter X., p. 462.

[5] Bohr, "Der respiratorische Stoffwechsel des Säugetierembryo," *Skand. Arch. d. Phys.*, vol. x., 1900; also vol. xv., 1904.

[6] Bohr, see Nagel's *Handbuch der Physiologie*, "Respiration," vol. i., H. i.

According to Liepmann,[7] the maternal blood contains a special protein, elaborated by the placenta, which may be recognised by the biological reaction, and Freund[1] states that a precipitable substance is present in the urine of pregnant women. Others have been unable to find such a substance either in the blood or urine (see Weichardt and Opitz[2]).

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[1] Hammett, "The Urea Content of Placentas from Normal and Toxæmic Pregnancies," *Jour. Biol. Chem.*, vol. xxxiv., 1918; "Urea Formation by the Placenta," *ibid.*, vol. iii., 1919.

[2] Nattan-Larrier, "Fonction Sécrétoire du Placenta," *Compt. Rend. Soc. Biol.*, vol. lii., 1900.

[3] See footnote [6], p. 557.

[4] Halban, "Die innere Secretion von Ovarium und Placenta, und ihre Bedeutung für die Function der Milchdrüse," *Arch. f. Gynäk.*, vol. lxxv., 1905.

[5] In future investigations, the better recognition of the composite structure of the placenta is desirable. In many animals it is possible to separate the maternal and fœtal tissues with considerable accuracy, and any effect obtained from one or other part can be definitely ascribed to the modified uterine mucous membrane, or to the extra-embryonic part of the ovum.

[6] Starling, "Chemical Correlations of the Functions of the Body," Croonian Lectures, *Lancet*, 1905. Starling appears, however, to have abandoned this theory in view of the more recent work on the functions of the corpus luteum (see p. 616).

[7] Liepmann, "Ueber ein für menschliche Plazenta spezifisches Serum," *Deut. med. Woch.*, 1902, 1903.

Veit's[3] theory is also *sub judice.* Taking up Schmorl's[4] discovery that emboli of placental cells may be found in organs of the mother in eclampsia, he extends it to normal pregnancy, and postulates that syncytial fragments and even whole villi pass regularly into the maternal circulation. There they give rise to an anti-body, a syncytiolysin, which itself dissolves the circulating syncytium. He also seeks to explain, by the activity of the lysin, the absorption of hæmoglobin and other proteins from the intervillous space by the villi, the pigmentation of the skin and vaginal mucous membrane from superficial emboli, and the phenomena of telegony from the circulation of elements derived in part from the paternal side.[5]

At present it is only a speculation, as Veit himself is careful to explain, but its far-reaching possibilities have already given rise to many investigations.[6] It must be clearly understood, however, that biologists have at present no convincing proof of the formation of an anti-body consequent on the introduction of *any* protein of the same individual, or one of the same species.

Abderhalden[7] claimed to have obtained evidence of the formation of specific ferments arising in the maternal organism as the result of the formation of the placenta. These ferments, which he calls "defensive ferments," were stated by him to have a specific action on the proteins of the placenta, and their formation was regarded by him to be the result of the reaction of the body against the presence of substances foreign to the blood. He elaborated a technique which renders it possible to recognise the presence of a placenta by the presence of these ferments; the so-called "Abderhalden reaction for the diagnosis of pregnancy." His claims, which he extended to various pathological conditions of other organs, were at first widely and somewhat uncritically accepted and gave rise to an extensive literature. They have, however, not stood the test of experimental criticism [1] and his views are no longer accepted.

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[1] Freund, "Beiträge zur Biologie der Schwangerschaft," *Vortr. auf d. 76 Naturf. zu Breslau*, 1904.

[2] Weichardt u. Opitz, "Zur Biochemie der Schwangerschaft," *Deut. med. Woch.*, 1903.

[3] Veit, "Ueber Deportation von Chorionzotten," *Zeitsch. f. Geb. u. Gynäk.*, vol. xliv. Also Veit u. Scholten, "Synzytiolyse und Hämolyse," *Zeitsch. f. Geb. u. Gynäk.*, vol. xlix., 1903.

[4] Schmorl, *Path.-Anat. Untersuchungen über die Puerperaleklampsia*, Leipzig, 1893.

[5] The discussion of the relationship between the deportation of chorionic villi and the pathology of eclampsia, pregnancy kidney, placental polypi, hyperemesis, etc., falls outside the scope of this work. A critical summary of recent work on this subject is given in *Medical Science*, vol. v., 1921, p. 537, in a review entitled "The Biochemistry of Eclampsia."

[6] See Kollmann, "Kreislauf der Plazenta, Chorionzotten und Telegonie," *Zeitsch. f. Biol.*, vol. xlii., 1901. Hinselmann, *Die angebliche physiologische Schwangerschaftsthrombose von Gefässen der uterinen Plazentarstelle*, Stuttgart (F. Euke), 1913.

[7] Abderhalden, *Abwehrfermente*, Berlin, J. Springer, 1914, 4th Edition.

From time to time evidence of hæmopoiesis in the placenta has been brought forward. Mention of it was first made by Masquelin and Swaen [2] in the rabbit, and later by Frommel [3] in the mouse and bat. Hubrecht [4] strongly upholds the occurrence of blood formation in the placentæ of *Tarsius* and *Tupaia*. The new erythrocytes arise as products of the fragmentation of nuclei of the trophoblast in *Tarsius* (see p. 440), and of the trophoblast, and probably also trophospongia, in *Tupaia* (see p. 485). They are later set free by solution of the surrounding protoplasm. Such a process is beneficial both to mother and embryo. The erythrocytes are increased at the expense of the ovum, and they in turn increase the supply of oxygen to the fœtus.

II. CHANGES IN THE METABOLISM OF THE MOTHER DURING PREGNANCY

General Considerations

How does the maternal organism react to the presence of a rapidly growing mass of tissue, namely the fœtus and adnexa? An idea of the food and energy requirements which the presence of the fœtus imposes upon the maternal organism can be formed from the following data. The table is a very condensed summary of the figures calculated or obtained by Hoffström [5] in his investigation on the human subject, a primigravida living on an unrestricted diet. The figures give the total amounts in grammes of nitrogen, phosphorus, calcium and magnesium actually present at given times in the fertilised ovum, *i.e.* the fœtus with adnexa, and also the amounts which have been retained per week by the fertilised ovum.

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[1] Bullock, "A Critical Study of the Basis of Abderhalden's Serum Reaction," *The Lancet*, i., p. 223, 1915. Van Slyke and others, "The Abderhalden Reaction," *Jour. Biol. Chem.*, vol. xxiii., 1915. Falls and Walker, "The Influence of Pregnancy on the Proteolytic Activity of Blood-Serum," *ibid.*, vol. xxxii., 1917. Hulton, "The Formation of Specific Proteoelastic Enzymes in Response to Introduction of Placenta," *ibid.*, vol. xxv., 1916. Jobling, Eggstein, and Petersen, "Serum Proteases and the Mechanism of the Abderhalden Reaction," *Jour. Exp. Med.*, vol. xxi., 1915.

[2] Masquelin and Swaen, "Développement du placenta maternel chez le lapin," *Bull. de l'Acad. Roy. de Belgique*, 1879.

[3] Frommel, *Ueber die Entwicklung der Placenta von Myotus murinus*, Wiesbaden, 1888.

[4] Placental hæmopoiesis is denied by many authorities, including Duval, Maximow, Nasius, and Nolf. For a complete review of the subject, see Hubrecht, "Ueber die Entwicklung der Placenta von *Tarsius* und *Tupaja*, nebst Bemerkungen über deren Bedeutung als haematopoietische Organe," *Internat. Congr. of Zool.*, Cambridge, 1898.

[5] Hoffström, "Ein Stoffwechseluntersuchung während der Schwangerschaft," *Skandin. Arch. f. Physiol.*, vol. xxiii., 1910.

Week of Pregnancy.	N.		P.		Ca.		Mg.	
	Content of Ovum.	Weekly Requirements of Ovum.	Content of Ovum.	Weekly Requirements of Ovum.	Content of Ovum.	Weekly Requirements of Ovum.	Content of Ovum.	Weekly Requirements of Ovum.
16	4·28	1·13	0·67	0·20	0·38	0·02	0·026	0·0016
20	8·81	1·82	1·47	0·25	2·03	0·43	0·095	0·0173
24	16·07	1·80	2·48	0·27	3·74	0·41	0·164	0·0175
28	23·28	6·87	3·58	1·28	5·39	2·09	0·234	0·0642
40	105·76	6·87	18·93	1·28	30·51	2·09	1·004	0·0642

Bar[1] has calculated the following figures for the human fœtus without adnexa.

Period.	Daily N Requirement.
Till 4 months - - - - - -	0·0013 gm.
During 4th month - - - - -	0·042 „
„ 5th „ - - - - -	0·155 „
„ 6th „ - - - - -	0·166 „
„ 7th „ - - - - -	0·198 „
„ 8th and 9th months - - -	0·945 „

The additional energy requirements have been determined by Murlin[2] for the pregnant dog and by Carpenter and Murlin[3] for the human subject. In a bitch weighing about 14 kg. during sexual rest the following figures were obtained during two different pregnancies three days before birth.

Condition.	Total Energy in Calories.	Total Weight of Puppies in Grammes.
Sexual rest after lactation - -	505·3	...
1st pregnancy, one puppy born -	551·3	280
2nd pregnancy, five puppies born -	763·8	1,560

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[1] Paul Bar, *Leçons de Pathologie obstétricale*, vol. ii., Paris, 1907 (Asselin et Houzeau, editeurs).

[2] Murlin, "Energy Metabolism of the Pregnant Dog," *Amer. Jour. of Physiol.*, vol. xxvi., 1910.

[3] Carpenter and Murlin, "Energy Metabolism of Mother and Child just before and just after Birth," *Archives of Int. Medicine*, vol. vii., 1911.

The extra energy production at the end of pregnancy is therefore proportional to the weight of the offspring to be delivered. The increase over the metabolism of the mother during sexual rest amounted to about ten per cent. in the first pregnancy and to as much as fifty per cent. in the second pregnancy with five puppies.

In the human subject, where the weight of the fœtus in proportion to that of the mother is much smaller, the energy metabolism expressed per kilogramme and hour is in the last month of pregnancy only four per cent. larger than for a woman in complete sexual rest: 0·99 Cal. per kg. and hour in the latter condition, 1·03 Cal. per kg. and hour in the pregnant woman. This quantitative difference must be borne in mind in comparing observations on pregnant dogs with those on human subjects. Whatever changes occur are likely to be more pronounced and acute in the dog.

Directly or indirectly the mother must provide the additional energy and food materials necessary for building up and maintaining the developing embryo. Does this entail a sacrifice on the part of the mother? At first sight one would conclude *a priori* that this must necessarily be the case. This idea gradually developed into the conception that pregnancy involved a pathological condition of the maternal organism, and a good deal of experimental evidence was adduced in support of the view that in pregnancy the oxidative processes in the organism are essentially different from the normal. This view found its extreme expression in the dictum of Massen[1] that "a pregnant woman is by the diminished oxidation brought into a condition of auto-intoxication very similar to that produced in an animal with an Eck's fistula," where the blood flows from the portal vein directly into the vena cava, without passing through the liver. Similarly, Ewing[2] speaks of a "liver of pregnancy" and holds that normal pregnancy produces changes, especially in the liver, "difficult to separate from the pathological."

But more recent observations, especially the magnificent work of Bar[3] and his collaborators, which has been confirmed in its main results and extended by the careful investigations of Hoffström[4] and Murlin,[5] have shown that in a normal pregnancy the maternal organism is very far from being in a pathological condition, and that both the experimental data which formed the basis of the pathological conception of pregnancy and the arguments on which it was built up were open to criticism.

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[1] Massen, *Proc. Soc. for Obstetrics and Gynæcology of St. Petersburg*, Feb. 1899; *Zeitsch. f. Geburtshülfe*, vol. x.; quoted from Bar, see below.

[2] Ewing, "The Pathogenesis of the Toxæmia of Pregnancy," *Amer. Jour. of Medical Sciences*, vol. cxxxix., 1910.

[3] Paul Bar, *loc. cit.*

[4] Hoffström, *loc. cit.*

[5] Murlin, "The Metabolism of Development," I., II., and III., *Amer. Jour. of Physiol.*, vol. xxvi., 1910; vol. xxvii., 1910; vol. xxviii., 1911. A summary of these papers is given in the paper by Murlin, "The Nutrition of the Embryo," *Trans. 15th Internat. Congress of Hygiene*, September 1912.

In a normal mother carrying a healthy fœtus and living on an adequate diet, pregnancy does not entail a sacrifice on the part of the mother. In the words of Bar: "L'étude de la balance azotée n'autorise pas a dire qu'en principe le gestation constitue une periode de sacrifice; elle montre au contraire qu'elle peut être et qu'elle est souvent une période de profit. La gestation apparaît donc comme un exemple de symbiose harmonique homogène."

The various aspects of the metabolism of pregnancy will now be discussed in greater detail.

A. *The Source of the Materials transferred to the New Organism*

The question is discussed in another chapter (see p. 509) whether the materials that go to the formation of the new organism are elaborated entirely in the new ovum itself, or are wholly prepared by the mother. As stated there, the histological and biological evidence leads us to believe that the materials, whatever their source and constitution, are in the early stages broken down and partly resynthesised by the trophoblast, while later in pregnancy they are metabolised by the fœtal cells themselves. Granting this, we must further suppose that the maternal duties do not extend to the formation of fœtal tissue-components, but are limited to the provision of food and oxygen for the fertilised ovum, the removal of its waste products and the preparation of an organ of nutrition for the new-born young. Each of these duties leads to changes in metabolism, which may, in addition, be excited by special stimuli produced during pregnancy (see p. 515).

In the provision of nutriment for the embryo, does the mother deplete her own tissues, or is she content to transfer the unorganised substances which are absorbed from the food and not yet fixed as vital constituents of the protoplasm? Probably both. In insufficient nutrition the mother certainly gives up organised tissue-products, and even with a plentiful diet a period has been observed in the dog in the earlier stages of pregnancy (see p. 527) during which the maternal organism loses nitrogen and therefore draws on its own tissues. On the other hand, in the later stages of pregnancy when the requirements of the fœtus are greatest there is on an adequate diet a considerable retention of nitrogen. This is brought about, as will be seen, by a more perfect assimilation of the absorbed food. At this stage, therefore, the unorganised substances of the absorbed food are apparently being utilised directly by the trophoblast. This conclusion finds confirmation in the observation that variations in diet are apparently capable of producing changes in the fœtus.[1] It was noted by Lochhead and Cramer[2] that abortion occurred in three out of six pregnant rabbits fed on a diet rich in carbohydrates during the whole period of gestation. A similar observation is recorded by Cramer and Marshall.[2] Wallace[3] states that cows fed on molasses prove to be uncertain breeders, and Heape[4] that Lincoln sheep fed solely on turnips are specially liable to abortion.

According to Noel Paton,[5] the size of the offspring of the guinea-pig depends very directly upon the diet and nutrition of the mother during pregnancy. "To the physiologist it demonstrates the limitations in the extent to which the tissues of the mother can be utilised for the construction of the embryo. The nourishment of the maternal tissues seems to take precedence over the nutrition of the fœtus. The mother appears to pass on the *surplus* nourishment to the fœtus. The better the nourishment of the maternal tissues, the greater the growth of the fœtus." This generalisation is too sweeping. Observations on rats[6] have shown that the weight of the offspring remained the same on different diets, although on one diet the mother increased in weight during pregnancy while on the other it lost in weight. Further, it has been proved in the pregnant rabbit that, when the glycogen of the body is reduced to traces by repeated injections of phloridzin, the placenta and fœtus still retain considerable amounts.[7] In this instance the needs of the fœtus have taken precedence over the storage of a carbohydrate reserve for the mother. Like Paton, Prochownick[8] states that the size of the offspring may be markedly diminished by restricting the diet of the mother (human female); but many exceptions to this rule are found, which in fact comes into operation only when the restriction of food has been severe enough to jeopardise the health of the mother.

This opens up another question: Does the expenditure for the embryo entail loss to the mother? "If the mother must transfer a part of her own bodily substance to the germ, the loss is of little importance if she can cover this loss from her food. The setting of the question runs thus: Is the maternal body deprived of protein, fat, and other substances during and in consequence of the formation of a new being, and is its store of these materials, after the resulting birth, or at the close of the puerperium, less than before the advent of pregnancy, or is this not the case? An unprejudiced clinical proof from human subjects points to the possible occurrence of both conditions. Many mothers during pregnancy increase so slightly in weight that their own tissues must have suffered loss during this time, others become heavier to the extent of ten kilograms or more. The investigation has not to determine whether the maternal organism suffers loss or experiences gain, but to demonstrate under which conditions of nourishment the one or the other appears. It has to investigate whether and in what amount the needs of the mother are increased, if her original condition is to remain unaltered while new tissues are being formed" (Magnus-Levy[1]).

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[1] Thiemich was, however, unable to discover any difference in the constitution of the fœtal fat, after feeding the mother on widely different fats (see p. 543).

[2] See Cramer and Marshall, "A Note on Abortion as a result of a Diet rich in Carbohydrates," *Jour. of Econ. Biol.*, vol. iii., 1908.

[3] Wallace, *Farm Live Stock*, 1907.

[4] Heape ascribes the frequency of abortion to the fouling of the turnip-roots by mud and excrement, a condition of things which results from overcrowding. See *Jour. Roy. Agric. Soc.*, 1899.

[5] Noel Paton, "The Influence of Diet in Pregnancy on the Weight of the Offspring," *Lancet*, 1903.

[6] Cramer (W.), Unpublished observations.

[7] Lochhead and Cramer, "The Glycogenic Changes in the Placenta and the Fœtus of the Pregnant Rabbit," *Proc. Roy. Soc. London*, B., vol. lxxx., 1908.

[8] Prochownick, *Therap. Monatshefte*, 1901, quoted by Paton (*loc. cit.*).

B. *The Body-weight during Pregnancy*

Systematic determinations of the body-weight give some idea of the effect of pregnancy on the maternal organism as a whole. Gassner[2] observed a progressive increase in weight, greater than the increase in the weight of the fœtus (about 1 kilo per month) and the generative organs (about 0·125 kilo per month) together. This is due to the increase in the other parts of the maternal organism as a "result of the inactivity and good dietetic conditions during pregnancy, and the frequency with which the tissue fluids, *e.g.* in the lower extremities, are increased." Baumm[3] confirmed these results. A diet necessary to maintain the body-weight in a woman of the same size gave an increase in weight of a pregnant woman amounting to an average of 1·777 kilo in thé last month, of which 0·650 kilo represented increase outside the fœtus and generative organs.

Zacharjewsky[4] observed an increase in weight running parallel to the increased weight of the fœtus and uterus. Some days before birth he found a decrease in primiparæ and a balance in multiparæ, which he referred to Ahlfeld's observations that the fœtus increases only up to the thirty-ninth week, and in the last week decreases.

There are, however, limitations to the estimation of the total metabolism by the alteration in weight. Thus Bar and Daunay[1] discovered no increase of weight in a pregnant dog, though it had retained 5·24 gm. nitrogen, equal to 170 gm. flesh. Similarly, Hoffström, in a primigravida, found a total retention of 209 gm. nitrogen during pregnancy which could not be accounted for by the slight increase in weight. Such a discrepancy may perhaps be explained, partly at any rate, by a loss of water. In Man the physiological variation in the water-content is as much as 2 kilos. And in Hoffström's case the slight increase in weight was accompanied by a loss of fat. In any case this unusual discrepancy between weight and nitrogen retention, which requires further explanation, indicates a remarkable alteration in the metabolism of the maternal organism. Hence it is necessary to obtain a more accurate measure, and for this purpose to investigate separately the metabolism of various substances: proteins, carbohydrates, fats, minerals, salts, and oxygen.

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[1] See v. Noorden, *Metabolism and Practical Medicine*, vol. i., section on "Metabolism of Pregnancy."

[2] Gassner, "Ueber die Veränderung des Körpergewichtes bei Schwangeren, etc.," *Monatsschr. f. Geburtsh. u. Frauenkrankh.*, vol. xix., 1862.

[3] Baumm, "Gewichtsveränderungen der Schwangeren, etc.," *Inaug.-Dissert.*, München, 1887.

[4] Zacharjewsky, "Ueber den Stickstoffwechsel während der letzten Tage der Schwangerschaft, etc.," *Zeitsch. f. Biol.*, vol. xxx., 1894.

C. *The Protein Metabolism in Pregnancy*

(*a*.) *The Absorption of Proteins by the Mother.*—According to Kehrer,[2] the gastric functions are slightly below normal in the human female during pregnancy. Free hydrochloric acid and pepsin are each decreased by a third. At the same time the intestinal functions appear to be sufficiently active for the satisfactory absorption of nutriment.

The absorption of flesh does not show any characteristic change in the dog during pregnancy. If decreased, it is due to pathological conditions, and diarrhœa and vomiting are present (Bar and Daunay). Ver Eeke[3] states that the absorption of nitrogen decreases in the second half of pregnancy in the rabbit, but he ascribes the change to mechanical conditions. Maurel[4] is of opinion that a gradual decrease in the nitrogen intake occurs throughout pregnancy in the guinea-pig, but at the beginning the intake is above the non-pregnant level. Zacharjewsky found that only four to six per cent. of the nitrogen was unabsorbed by the human female in the last two weeks of pregnancy, and Slemons[5] found seven per cent. and three per cent. in a primipara and a multipara respectively at the same period. The observations of Hoffström in a primipara during the last six months of pregnancy showed an absorption of protein, and indeed of all the food-stuffs, as good as in the normal person. It was in fact slightly better than the standard given by Atwater.

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[1] Bar and Daunay, "Bilan des échanges azotés pendant la grossesse," *Jour. de Phys. et de Path.*, vol. vii., 1905.

[2] Kehrer, *Die physiologischen und pathologischen Beziehungen der weiblichen Sexualorgane zum Tractus intestinalis*, Berlin, 1905.

[3] Ver Eeke, *Lois des échanges nutritifs pendant la gestation*, Bruxelles, 1901.

[4] Maurel, "Des dépenses albuminoides pendant la grossesse chez le cobaye," *Compt. Rend. Soc. Biol.*, vol. lxi., 1907.

[5] Slemons, "Metabolism during Pregnancy, Labour, and Puerperium," *Johns Hopkins Hosp. Rep.*, vol. xii., 1904.

(*b.*) *The Daily Requirement of Protein for the Fœtus.*—The only measure we possess of the extra protein required in pregnancy is the amount deposited in the fœtus and adnexa, the growing uterus and mammæ. But this gives too low a figure, since 1 gm. of tissue-protein requires more than 1 gm. of food-protein for its manufacture. In addition, though we are dealing with a period when anabolic processes are at a maximum in the new organism, we are bound to assume that the cardiac, hepatic, and other activities of the fœtus, and the rhythmic contractions of the uterus, entail a certain loss of protein from wear and tear. Whether protein substances play any part in the provision of energy for the work of organisation is not known. In so far as the work of organisation is carried out by the mammalian fœtus and not by the mother, the energy is probably supplied by the combustion of carbohydrates alone (see p. 553). Murlin has calculated in dogs the total energy requirements of the fœtus. He finds the total metabolism per unit of weight of the embryos three days before birth equal to three times the metabolism of the mother dog.

The amount of nitrogenous material deposited in the human fœtus during the last stages of pregnancy has been calculated. Michel[1] estimates it at 56·69 gm. of nitrogen in two months, or slightly under 1 gm. per day. Similar figures were obtained by Fehling.[2] Magnus-Levy's figures are somewhat lower—50 gm. in the last hundred days, or 0·5 gm. per day. This represents only 3 gm. of protein, and when added to the daily deposition in the placenta, uterus, and mammæ, it still remains relatively inconsiderable. The calculations of Bar and of Hoffström have already been given in tabular form (see p. 519).

(*c.*) *The Nitrogen Balance in Pregnancy.*[3]—According to the earlier investigators, a special economy of protein exists during pregnancy. As Repreff[4] puts it, anabolic processes are increased and katabolic processes decreased in pregnancy in dogs, rabbits, and guinea-pigs.

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[1] Michel, "Sur la composition chimique de l'embryon et du fœtus humain," *Compt. Rend. Soc. Biol.*, vol. li., 1899.

[2] Fehling, "Beiträge zur Physiologie des placentaren Stoffwechsels," *Arch. f. Gynäk.*, vol. xi., 1877.

[3] See also Magnus-Levy in v. Noorden's *Metabolism and Practical Medicine*, vol. i., Sect. IV. D., English Translation, 1907; and Leo Zuntz in Oppenheimer's *Handbuch d. Biochemie*, Erganzungsband, 1913.

[4] Repreff, "De l'influence de la gestation sur les échanges materiels," *Russ. Dissert.*, 1888. Quoted by Slemons, *loc. cit.*

Hagemann's[1] investigations in the dog form the first accurate observations of the nitrogen balance during the whole course of pregnancy. He set himself to solve the question whether the new organism was formed from the food, or at the expense of the maternal tissues. From the first experiment he concluded that, even on a diet rich in nitrogen, there was a loss of protein to the mother at the end of pregnancy. While 33·583 gm. nitrogen were retained, the young contained at birth 7·445 gm. This left a balance of 26·128 gm. for the extra needs of the mother, which, he says, was nearly all required for the formation of the fœtuses (calculated at 16·6 gm.) and placentæ (8·7 gm.). The additional nitrogen required for the growth of the uterus and mammæ must have been derived from the maternal tissues. Hence the pregnancy resulted in a loss to the mother. Similarly, in lactation 34·056 gm. nitrogen were retained, and the calculated excretion in the milk was 76 gm.—a loss of 41·944 gm. nitrogen.

Later work has shown that this conclusion is not warranted, but the figures have been given in some detail to illustrate some of the difficulties to be overcome in carrying out the investigation. Many troubles have been experienced in trying to keep the animals on a constant diet, and, in addition, the increasing size of the uterus may prove a mechanical difficulty and impede the intestinal activity (Ver Eeke[2]). Hagemann failed to obtain the shed placentæ, which were eaten by the mother animal. Hence the estimate of 8·7 gm. nitrogen lost by them during pregnancy and labour is arbitrary, and is, according to Bar and Daunay,[3] much too high. On these and other grounds—there is a period of thirteen days during the pregnancy for which no data are given—the calculations for pregnancy considered as a unit are open to objection.

On one point the results are of value. Hagemann states that the period of gestation may be divided into two parts. In the first, which lasts in his experiment for the first month of pregnancy, there is a continuous loss of nitrogen to the mother each day. In the second, there is a storage of nitrogen which is used in the growth of the product of conception.

In Ver Eeke's experiments, nineteen in all, on the rabbit, two phases were also frequently observed, but the results varied widely. In some there was a positive balance throughout, and in others a negative balance now at one time and now at another. In the greater number the same diet was administered before and after pregnancy and during its whole course. The amount of protein did not far exceed the minimal requirement for the maintenance of nitrogenous equilibrium.

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[1] Hagemann, "Ueber Eiweissumsatz während der Schwangerschaft und Laktation," *Arch. f. Anat. u. Phys.*, Phys. Abth., 1890; also *Inaug.-Diss.*, Erlangen, 1891.

[2] Ver Eeke, *Lois des échanges nutritifs pendant la gestation*, Bruxelles, 1901.

[3] Bar and Daunay, "Bilan des échanges azotés pendant la grossesse," *Jour. de Phys. et de Path.*, vol. vii., 1905.

Similarly, variable results were obtained by Jägerroos[1] in the dog.[2] In his Experiment II., in which the nitrogen content of the food was high and the diet was pure flesh, there was a positive balance each week except the second, 27·9 gm. nitrogen in all being retained during pregnancy. In Experiment III., also on a diet of flesh but containing only 5·97 gm. nitrogen per day, a negative balance occurred only in the fifth and sixth weeks; but when the weight of the fœtuses and adnexa, and a serious loss of nitrogen soon after labour were deducted, there was a final loss to the mother of more than 6 gm. of protein. In the last experiment the diet consisted of 60 gm. of flesh and 100 gm. of sugar, which was just sufficient to maintain nitrogenous equilibrium.[3] It was maintained for the first few days of pregnancy, and then a loss of nitrogen occurred each week throughout the whole course of gestation except the third.

Bar has criticised—and rightly so—the diet given by Jägerroos as unsuitable. The animals did not take the food well, so that at times there was more nitrogen in the excreta alone than in the food. From his criticism and his own observations it is clear that Hagemann's dictum that gestation entails a sacrifice of protein on the part of the maternal organism holds good only when the animal is on an inadequate or unsuitable diet. Bar and Daunay[4] fed three pregnant bitches on a constant diet of bread, water, fat, beef, and salt, and estimated the nitrogen of the urine and fæces at regular intervals. They took precautions to secure the young and the after-births, and were able to determine accurately their nitrogenous content. In the three animals, as in two observed by Jägerroos, the period of gestation was triphasic. There was first a period of retention of nitrogen, then a balance or very slight loss, and finally a retention increasing with the progress of gestation. Further, there was over all a gain of nitrogen in two dogs at the conclusion of labour. Hence they conclude that pregnancy in a healthy animal, with a rational and sufficient diet, does not necessitate a drain on her stock of nitrogen to satisfy the needs of the fœtus.

The extensive work of Murlin on the metabolism of pregnancy also comprises observations on the nitrogen metabolism. These observations on four pregnant dogs, though carried out a few years after the publication of Bar's work, were completed without any knowledge of it. They led to essentially the same conclusion, namely that pregnancy is not necessarily associated with a loss of nitrogen by the maternal organism and does not therefore entail a sacrifice on the part of the mother—"a sacrifice on the part of the individual for the good of the species"—as the earlier observers had believed. On a suitable diet the mother may actually have retained considerable amounts of nitrogen at the end of pregnancy. The nitrogen retention does not, however, proceed evenly throughout pregnancy. Both in Murlin's and in Bar's animals it was most pronounced when one would least expect it, namely in the second half of pregnancy, when the demands of the fœtus are greatest. This increased nitrogen retention is associated with a diminished nitrogen excretion in the urine. In the first half of pregnancy the nitrogen retention is much less pronounced and there may actually be a nitrogen loss, indicating an increased protein katabolism.

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[1] Jägerroos, "Der Eiweiss-, Phosphor-, und Salzumsatz während der Gravidität," *Arch. f. Gynäk.*, vol. lxvii., 1903.

[2] Jägerroos and Ver Eeke failed to secure the shed placentæ.

[3] Calculated over two days only.

[4] Bar and Daunay, *loc. cit.* Bar, *loc. cit.*

Bar distinguishes, therefore, in the pregnant dog two distinct periods of about equal length. The first period, when the needs of the embryo in nitrogen are small, is characterised by a tendency to loss of nitrogen on the part of the mother. This lasts to the middle of pregnancy (the thirtieth day in the dog) when the second period of distinct nitrogen retention sets in. Bar has noted further that during the first period gastro-intestinal disturbances occur in the dog, and has made the interesting suggestion that this period of nitrogen loss coincides with the period of morning sickness with women. Now in the dog the placenta is fully matured at about the thirtieth day of gestation, in human pregnancy it is fully developed at the end of the fourth month. Further, Graefenberg[1] has shown that the chorionic villi of the human placenta during the first three months of pregnancy contain a proteolytic enzyme, the seat of which he ascribes to the Langhans cells. This ferment weakens during the fourth month and disappears in the fifth. This, coupled with the fact that the serum of pregnant women has a greatly increased content of anti-trypsin from the beginning of pregnancy on, is taken to indicate that these proteolytic enzymes pass into the maternal organism, which protects itself by the formation of anti-trypsin. It has been suggested, therefore, that the period of protein katabolism is due to the formation of proteolytic enzymes by the developing trophoblast and the passage of these enzymes into the maternal organism. When the placenta is fully formed the passage of these enzymes into the maternal organism ceases, and with it the increased protein katabolism.

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[1] Graefenberg, "Der Antitrypsingehalt des mütterlichen Blutserums während der Schwangerschaft," *Münchener med. Woch.*, vol. lvi., 1909; "Beiträge zur Physiologie der Eieinbettung," *Zeitsch. f. Geburtsh. u. Gyn.*, vol. lxv., 1909.

At present this suggestion must be looked upon as an interesting speculation. It still remains to be shown that the introduction of weak proteolytic ferments produces an increased protein katabolism. It is also obvious that gastro-intestinal disturbances must necessarily interfere with the intake and the absorption of food, and may in themselves be an adequate explanation of the diminished nitrogen retention. There is, moreover, one criticism which applies to all the metabolism experiments on pregnant dogs, with the exception of those of Bar and Daunay. At the time when these observations were made the existence of specific accessory food factors in nutrition—the so-called vitamins—was not known.

One of the vitamins—the "water-soluble vitamin B"—has a special relation to nutrition. If it is completely absent from the food the animal loses in weight and eventually dies in a state of complete emaciation. It has been shown recently[1] that this is due to an atrophy of the lymphoid tissue which normally plays an important part in the absorption or assimilation of food. There is also an impairment in the functional activity of the intestinal epithelium and of the digestive glands leading to interference with the absorption of food. If only very small amounts of this vitamin are present the animal remains in good health, but an abundant supply of it has a distinctly favourable effect on the nutritive condition. In terms of metabolism experiments: the retention of nitrogen is dependent partly on the amount of the water-soluble vitamin present in the diet, in the sense that an abundant supply of this vitamin favours it. The desire to keep the composition of the food constant in metabolism experiments has led unintentionally to the choice of diets poor in vitamins. Thus in almost all the experiments the diet consisted of lean meat, which is poor in the water-soluble vitamin, either alone or with lard, which also is poor in this vitamin, and cane sugar which does not contain any. Bar's diet, in which bread was given with meat, was the only one which from the point of view of vitamin-content was adequate, although by no means ideal. And Bar's dogs showed the best nitrogen retention, although the amount of protein given was much less than in the experiments of those workers who had obtained a negative N balance.

In order to settle this important point of the importance of vitamins in pregnancy, experiments have been carried out in rats.[2] These were kept on a natural diet of bread, rice, and maize, which, though not rich in vitamins, is adequate to maintain the animals in good health and enables them to grow and to breed. On this diet the mother just managed to maintain its weight at the end of pregnancy. But when this diet is supplemented by yeast preparations which are rich in the water-soluble vitamin, then the mother always showed a considerable gain of weight during pregnancy. The weights of the fœtus were not affected. These observations show very clearly the importance of an abundant supply of vitamin during pregnancy for the protection of the maternal organism. They also demand a repetition of the metabolism experiments on dogs with an abundant supply of vitamins in the food, before it can be accepted as definitely established that a period of increased protein breakdown is a regular feature of the early period of pregnancy. What can be regarded as definitely established is the fact that the maternal organism is capable of adapting itself to the requirements of the growing fœtus, and that this adaptation is so efficient that the maternal organism itself gains by it.

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[1] Cramer, Drew, and Mottram, "The Function of the Lymphocyte and of Lymphoid Tissue, in relation to Nutrition," *The Lancet*, 1921. "Intestinal Absorption, Vitamins, and Radium," *Brit. Jour. Exp. Pathol.*, 1922, vol. iii.

[2] Cramer (W.), Unpublished observations.

This remarkable retention of nitrogen during pregnancy is probably a preparation for the period of lactation. The energy requirements of the new-born are, as Murlin showed, very much higher than those of the embryo immediately before birth. This is due to the fact that the new-born has to maintain its body temperature against a colder environment. In Cramer's experiments on rats it was found accordingly that the mother, who has to provide for a litter of six to nine young ones, always loses in weight considerably during the period of lactation, even when the diet is very rich in vitamins. But in the latter case this loss does not exceed the gain in weight acquired during pregnancy. On a diet more restricted in vitamins the weight of the mother at the end of lactation was always considerably below that at the time of conception. These findings suggest the possibility that in the human subject the supply of vitamins may be a factor determining the capacity to nurse.

In the human female a nitrogen retention has been found frequently. Most of these observations could be carried out only during the last few weeks of pregnancy. The careful and complete observations of Zacharjewsky[1] during the last few days of pregnancy are the first contribution to the problem. He found a gain of nitrogen of 0·873 gm. per diem in primiparæ and 5·05 gm. in multiparæ. Similar results were obtained by Schrader,[2] by Moris Slemons,[3] and by Hahl.[4] Observations during the earlier periods of pregnancy were made by Sillevis[1] on three primiparæ and refer to the twenty-eighth week, the thirty-fourth week, and the thirty-eighth week of pregnancy. In every case he found a nitrogen retention which amounted to an average of 2 gm. per diem. The work of Bar[2] contains observations on ten women during the end of pregnancy. Of these, nine showed a nitrogen retention which varied from 2·26 to 7·50 gm. per diem in different individuals. The tenth woman suffered from intestinal disturbances during which she suffered a nitrogen loss. Some of the subjects of his observations were examined later when not pregnant and showed on the same diet a much smaller retention of nitrogen.

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[1] Zacharjewsky, "Über den Stickstoffwechsel während der letzten Tage der Schwangerschaft," *Zeitsch. f. Biol. N.F.*, vol. xii., 1894.

[2] Schrader, "Untersuchungen über den Stoffwechsel während der Schwangerschaft und im Wochenbett," *Arch. f. Gynäk.*, vol. lx., 1900.

[3] Slemons, *loc. cit.*

[4] Hahl, "Beiträge zur Kenntniss des Stoffwechsels während der Schwangerschaft," *Arch. f. Gynäk.*, vol. lxxv., 1905.

The amount of nitrogen which is used by the fœtus and the genital organs is calculated by Bar to be 1·5 gm. per diem, so that a normal pregnant woman on an adequate diet retains more nitrogen than is required by the fœtus with adnexa, the uterus and the mammary gland. The mother adds, therefore, to her own store of nitrogen. For this reason Bar describes the condition of pregnancy as "une symbiose harmonique homogène : l'organisme maternel fournissant au fœtus le moyen de se développer, et cela aux seuls dépens de ce qui dans la ration deviendrait matière excrémentitielle, sans rien perdre par conséquent. Par suite de l'adaptation de sa nutrition aux exigences nouvelles, la mère loin d'être lesée semble souvent utiliser pour elle-même une partie de l'albumine, qui lui apporte une ration, faite d'instinct plus abondante et mieux utilisée dans l'intestin."

The most prolonged investigation on the human subject is that of Hoffström[3] who kept a primipara under continuous observation from the sixteenth week on till the end of pregnancy. With a varied diet he obtained the comparatively low nitrogen intake of 13 gm. per diem on the average, with daily variations of a minimum of 10 gm. and a maximum of 16 gm. On this diet he obtained throughout the whole period of observation a nitrogen retention of an average of 1·84 gm. per diem, or fourteen per cent. of the nitrogen intake. The total amount retained was 310 gm. N, of which 101 gm. were deviated to the developing ovum. The maternal organism completed, therefore, the pregnancy with the remarkable net gain of 209 gm. nitrogen. It is equally remarkable that the body weight of the mother only increased by 550 gm. Very similar results were obtained by Landsberg[4] on several women. It must, therefore, be accepted as a fact that in pregnancy the mother retains nitrogen in amounts quite out of proportion to its increase in body weight. In what form this nitrogen is retained is not yet clear. The nitrogen retention does not proceed evenly throughout pregnancy, but is most marked in the second half of pregnancy, so that we have a confirmation of the paradox observed by Bar in dogs that the nitrogen retention is greatest when the requirements of the fœtus are highest. The increased retention is due to diminished excretion in the urine. It follows, therefore, that in a normal pregnancy the maternal organism improves its capacity for retaining nitrogenous material, and as we shall see presently, also inorganic materials. The observations of Hoffström have been confirmed by Wilson,[1] who also found a retention of nitrogen in excess of the requirements of both the fœtus and the mammary glands and genitalia of the mother. The store of nitrogenous material is apparently a reserve which is drawn upon and exhausted during the puerperium and lactation. It has been shown recently[2] that the retention of nitrogen is associated with the functional activity of the lymphoid tissue. If the latter is atrophied the organism loses nitrogen and the animal emaciates. If the lymphoid tissue is very active, there is a greatly increased nitrogen retention. It is possible that the increased nitrogen retention in pregnancy is associated with the leucocytosis of pregnancy which has been observed frequently (see below, p. 556). This suggestion finds confirmation in the observation referred to above, that a gain in weight during pregnancy of the maternal organism can be ensured by an abundant supply in the diet of the water-soluble vitamin which stimulates the functional activity of lymphoid tissue.

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[1] Sillevis, "Jets over de Stofwisseling der Gravida," *Akad. Poefschrift.* Leyden, 1903. Abstracted in *Mon. f. Geburtshülfe*, p. 240, 1905; quoted from Bar.

[2] Bar, *loc. cit.*

[3] Hoffström, *loc. cit.*

[4] Landsberg, "Untersuchungen über den Stoffwechsel bei Schwangeren," *Zeitsch. f. Geburtsh. u. Gynaekol.*, vol. lxxi., 1912.

(*d.*) *The Excretion of Nitrogen during Pregnancy and its Distribution in the Urine.*—It has just been stated that the excretion of nitrogen diminishes as pregnancy progresses. The excretion by the intestine remained constant in Hoffström's case. Bar's observations on dogs also showed that the fæcal nitrogen was, if anything, diminished. This indicates that the absorption and utilisation of food by the intestine remains good during a normal pregnancy. The excretion of nitrogen by the urine is diminished, and it is by virtue of this diminution that the maternal organism retains increasing amounts of nitrogen. This is due to a diminished excretion of urea in the urine, as both Bar and Murlin showed. The result is an alteration of the nitrogen distribution in the urine: the percentage of nitrogen excreted in the form of urea is diminished, the percentage excreted in the form of ammonia, the so-called "ammonia index" or "ammonia coefficient," is increased. It must be clearly understood that this percentage increase in the ammonia nitrogen and decrease in the urea nitrogen refer to the relative proportion of nitrogen excreted as these two substances and not to the absolute amounts excreted, which are diminished. The amino-acid nitrogen was found by Leersum[1] in forty per cent. of pregnant women on the hospital diet to amount to ten per cent. and more of the total nitrogen, whereas it varies between 2·7 and 7·7 per cent. in the non-pregnant. Similar high figures were obtained by Murlin. Wilson[2] also found an increase in the amino-acid nitrogen. Polypeptides have also been observed.[3] The occurrence of creatin in the urine of normal pregnant women on a creatin-free diet was first demonstrated by Krause and Cramer[4] and confirmed by other workers.[5]

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[1] Wilson (K. M.), "Nitrogenous Metabolism in Pregnancy," *Johns Hopkins Hosp. Bull.*, vol. xxvii., 1916.

[2] Cramer, Drew, and Mottram, *loc. cit.*

These facts have been the chief support of the idea referred to above (see p. 520), that even in normal pregnancy the metabolism is faulty; the high ammonia-nitrogen percentage has been interpreted as indicating an acidosis, the high amino-acid nitrogen was taken as a sign of hepatic insufficiency in the sense that the power of the liver to split off ammonia from the amino-acids of the proteins was impaired. The presence of creatin was looked upon by some authors as a confirmation of the existence of hepatic insufficiency. Further confirmation was believed to be presented by the change in the distribution of the sulphur in the urine. The inorganic sulphate sulphur was low in percentage like the urea nitrogen, the unoxidised or neutral sulphur was increased.[6] This was interpreted by Hoffström as a diminished power of oxidation on the part of the mother. From this point of view the toxæmias of pregnancy and eclampsia, in which very high values for the percentage of ammonia nitrogen had been found, appeared merely as an exaggeration of a pathological metabolism which exists throughout pregnancy.[7] In 1912 Murlin[8] wrote: "This theory has obtained so firm a foothold that to-day many obstetricians consider it an additional reason why chloroform should not be used as an anæsthetic and its use limited in normal labour, for it has been shown that this drug produces a degeneration of the liver cells and therefore might prove synergistic to a condition of toxæmia which is already present, but the symptoms of which are latent." Examination of the nitrogen distribution in the urine was looked upon as an important index of an impending toxæmia. And one authority went so far as to state that when the ammonia nitrogen rose to ten per cent. of the total nitrogen and vomiting had been present in the early months, emptying the uterus was indicated.

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[1] Leersum, "Die Ausscheidung von Aminosäuren während der Schwangerschaft," *Biochem. Zeitsch.*, 1908, Festschr. f. Hamburger.

[2] Wilson (K. M.), "Nitrogenous Metabolism in Pregnancy," *Johns Hopkins Hosp. Bull.*, vol. xxvii., 1916.

[3] Falk and Hesky, "Ueber Ammoniak, Aminosäuren und Peptid-Stickstoff im Harn Gravider," *Zeitsch. f. klin. Med.*, vol. lxxi., 1910.

[4] Krause and Cramer, "The Occurrence of Creatin in Diabetic Urine," *Proc. Phys. Soc.*, *Jour. of Physiol.*, vol. xl., 1910.

[5] Van Hoogenhuyze and Doeschate, "Recherches sur les échanges organiques chez les femmes enceintes," *Ann. de Gyn. et d'Obstetr.*, vol. xxxviii., 1911.

[6] Hoffström, *loc. cit.* Murlin, *loc. cit.*

[7] Ewing and Wolf, "The Metabolism in the Toxæmia of Pregnancy," *Amer. Jour. Obstet.*, vol. lv., 1907.

[8] Murlin and Bailey, "Protein Metabolism in late Pregnancy and the Puerperium," *Jour. Amer. Med. Ass.*, vol. lix., 1912.

The extensive observations of Murlin[1] on the composition of the urine in pregnancy, both in dogs and the human female, have thrown doubt on this view of normal pregnancy as a pathological condition. According to Murlin this view is based on a misconception of the significance of the observed changes in the nitrogen distribution. He also showed that the very high figures for the ammonia excretion in eclampsia which have been obtained are due to the fact that in this condition the urine has to be drawn with a catheter and that even in the most experienced hands it is impossible to avoid introducing into the bladder bacteria capable of decomposing the urine in the bladder. With all the clinical signs of pre-eclampsia the nitrogen partition may be normal up to the development of convulsions and even during the twenty-four hours following it. From analyses of 100 cases he concluded that the average of the nitrogen distribution in the last month of normal pregnancy does not markedly differ from the normal non-pregnant condition. In individual normal cases the ammonia nitrogen may rise to seventeen per cent. and the amino-acid undetermined nitrogen to ten per cent. of the total nitrogen. But this does not necessarily indicate an acidosis or an abnormal condition. It is the result of the increased retention of nitrogen. In a normal non-pregnant organism the bulk of the urea excreted represents waste or excess nitrogen, which is split, off and got rid of as urea. During the end of pregnancy increasing amounts of this waste nitrogen are being used up, as has been seen, by the mother for the fœtus and for its own tissues. Consequently the excretion of total nitrogen and of urea falls and if the absolute amounts of ammonia excreted remain unaltered, its relative amount is bound to increase, *i.e.* the "ammonia index" rises. The same argument applies to the change in the relative amounts of sulphates and neutral sulphur excreted in the urine.

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[1] Murlin, "Qualitative Effects of Pregnancy on the Protein Metabolism of the Dog," *Amer. Jour. Physiol.*; vol. xxviii., 1911. Murlin and Bailey, *loc. cit.* Murlin, "Observations on the Protein Metabolism of Normal Pregnancy and the Normal Puerperium," *Surgery, Gynecology and Obstetrics*, 1913.

Murlin has pointed out that some of the high ammonia indices obtained in eclampsia and also in normal pregnancies are due to decomposition occurring in the bladder, when a catheter has been used. Even with the strictest aseptic precautions it is impossible to prevent a plug of mucus being pushed into the bladder. Catharsis is another factor which may raise the ammonia index considerably by temporarily lowering the nitrogen intake.

There is no doubt that in abnormal pregnancies, particularly in the pernicious vomiting of pregnancy, there is an actual increase both in the relative and in the absolute amounts of ammonia excreted. The ammonia index may rise to 30, 40 and even 70 against the normal index of 4 to 8. But this condition necessarily involves a low nitrogen intake which may amount to starvation. This in itself raises the ammonia index. In addition, there is frequently, if not always, a formation of considerable amounts of aceto-acetic acid and oxybutyric acid which lead to an increased excretion of ammonia and thus raise the ammonia index. It has been suggested that the high ammonia excretion is due primarily to a faulty protein metabolism which is specific for pregnancy. But the formation of the acetone bodies is in itself an adequate explanation of the increased ammonia excretion, and it is difficult to understand why so many observers refuse to attach any importance to the presence of these substances. It is even more difficult to understand why some workers have carried this neglect so far that they record long tables of analyses for the nitrogen distribution of the urine which show exceptionally high values for the ammonia index and completely omit even to test qualitatively for the presence of the acetone bodies. The only observations which have paid due attention to this point are those of Gilliatt and Kennaway[1] who found a close parallelism to exist between the amount of the acetone bodies present and the ammonia excretion. The amount of acetone bodies present in their cases was too high to be accounted for as a direct result of starvation. They are inclined to look upon the excessive formation of these bodies as the primary cause of the condition, and draw an analogy with the similar conditions of cyclic vomiting in children. The point is of some practical importance, because a persistent high ammonia index is regarded by many authorities as an indication for emptying the uterus. The ammonia index can only be determined by a skilled worker in a special laboratory, and for its proper appreciation requires a knowledge of the total nitrogen intake of the patient, *i.e.* a collection of the urine excreted for twenty-four hours. A good estimate of the amount of acetone bodies present can be obtained in a few minutes by the proper application of Rothera's test, and a test-tube is the only apparatus required.

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[1] Gilliatt and Kennaway, "Some Observations upon Cases of Vomiting in Pregnancy," *Quar. Jour. Medicine*, vol. xii., 1918. This paper contains also a critical survey of the literature on the metabolism in this condition.

Other aspects of the acid-base equilibrium during pregnancy will be dealt with below in a separate section.

The only feature of the urine of pregnancy which could not be explained satisfactorily by Murlin was the presence of creatin. Folin, as a result of his observations on the composition of the urine of normal adult men, had stated that on a creatin-free diet creatin is absent from normal urine. This statement was generally accepted, and the excretion of creatin in the urine was therefore taken as a sign of an abnormal metabolism, and far-reaching speculations were based on it. These speculations were deprived of their basis, at least so far as pregnancy is concerned, when it was found that normal women frequently and children always excrete creatin, even when on a creatin-free diet.[1]

Post-partum there is a rise in the excretion of total nitrogen which is independent of the food. It occurs rather suddenly at about the sixth or seventh day. There is also an increase in the excretion of creatin. These changes are probably related, as Murlin suggests, to the involution of the uterus.

The albuminuria of pregnancy in the human female is not strictly physiological. Regarding its frequency very varying figures have been given, ranging from five per cent. to sixty per cent. It appears in the second half of pregnancy, gradually increases up to the time of birth, and quickly decreases in the puerperium. In fifty per cent. of the cases it has already disappeared on the fourth day after labour. The protein is of renal origin, and in a typical case amounts to 0·01 to 0·05 per cent. That it is not due to mechanical pressure on the renal vessels or ureter, or to increased intra-abdominal pressure seems certain. Nor has any definite proof been given of the influence of a toxin arising in the fœtus, and causing degeneration of the renal epithelium. Veit[2] explains it by his hypothesis of the presence of placental constituents in the maternal circulation. Metabolic investigations in pregnancy complicated by albuminuria show nothing characteristic (Magnus-Levy[3]).

A special constituent of the urine may be found during the puerperium. Though called peptone (Fischel[4]), it really consists of deutero-albumoses which arise from the involution, *i.e.* autolysis, of the uterus (Langstein and Neubauer[1]). As with similar proteins introduced subcutaneously, the organism has not the power of splitting them up, and they are excreted unchanged. Fischel stated that peptonuria might also occur in pregnancy; but this was disproved by Thomson,[2] who also showed that a puerperal peptonuria did not regularly exist. Ehrström[3] regards it as a certain indication of fever and sepsis, the peptone being contained in the leucocytes of the purulent lochia.

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[1] Krause and Cramer, "Sex and Metabolism," *Proc. Phys. Soc.*, *Jour. of Physiol.*, vol. xlii., 1911. Krause, "On the Urine of Women under Normal Conditions, etc.," *Quar. Jour. Exp. Phys.*, vol. iv., 1911. Krause, "On Age and Metabolism and on the Significance of the Excretion of Creatin," *ibid.*, vol. vii., 1913.

[2] Veit, "Ueber Albuminurie in der Schwangerschaft," *Berlin klin. Woch.*, 1920.

[3] Magnus-Levy, see v. Noorden, *loc. cit.*

[4] Fischel, "Peptongehalt der Lochien," *Arch. f. Gynäk.*, vols. xxiv. and xxvi.

D. *The Carbohydrate Metabolism in Pregnancy*

(*a.*) *The Absorption of Carbohydrates by the Mother.*—The starch digestion is said to be retarded in the stomach during pregnancy (Kehrer[4]). Little is known regarding the absorption of carbohydrates, but there is evidence of a tendency to abortion in certain animals on a diet containing them in excess (see p. 522).

(*b.*) *Carbohydrates of the Maternal Organism.*—Lactose may appear in the blood in pregnancy as well as during the lactation period. Lævulose is not present in the serum of a healthy animal; but it is normally present in the allantoic fluid of the cow (Gürber and Grünbaum[5]), and in the blood-serum of the fœtal rabbit, cow, and sheep (Paton[6]). Whether it is the only monosaccharide present has not yet been determined, but it is in sufficient amount to render the serum lævo-rotatory. The proof that the carbohydrate is lævulose rests on the lævo-rotation of the plane of polarised light and the ketone reaction. Doubts have recently been expressed regarding the sufficiency of these two tests.

The glycogen store of the liver is stated to be increased in pregnancy in the dog (Burlando[7]), in the guinea-pig (Maurel[8]), and in the human female (Charrin and Guillemont[1]). But since the amount of glycogen varies greatly and is dependent to a large extent on the diet, it is difficult to establish with certainty that there is an increase. Harding,[2] on the other hand, postulates a greater tendency to a deficiency of glycogen in the maternal liver and associates this deficiency with the morning sickness of women and even with pernicious vomiting. This view is based on the work of Bohr and of Lochhead and Cramer,[3] who showed that the presence of the fœtal cells imposes a special demand for carbohydrates on the maternal organism. The pregnant woman has therefore a greater tendency to pass into a state of specific carbohydrate starvation than the non-pregnant woman. The important practical application of this fact will be discussed in greater detail below (see p. 544).

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[1] Langstein and Neubauer, "Autolyse des puerperalen Uterus," *Münch. med. Woch.*, 1902.

[2] Thomson (H.), "Ueber Peptonurie in der Schwangerschaft und im Wochenbett," *Deutsche med. Woch.*, 1889.

[3] Ehrström, "Puerperale Peptonurie," *Arch. f. Gynäk.*, vol. lxiii., 1901.

[4] Kehrer, *Die physiologischen und pathologischen Beziehungen der weiblichen Sexualorgane zum Tractus Intestinalis*, Berlin, 1905.

[5] Gürber and Grünbaum, "Ueber das Vorkommen von Lävulose im Fruchtwasser," *Münch. med. Woch.*, 1904.

[6] Paton, Watson (B. P.), and Kerr, "On the Source of the Amniotic and Allantoic Fluids in Mammals," *Trans. Roy. Soc. Edin.*, vol. xlvi., 1907.

[7] Burlando, "Behaviour of Hepatic Glycogen during Menstruation, Pregnancy, Puerperium, and Lactation Period," *Arch. Ital. di Ginec.*, 1906.

[8] Maurel, "Des dépenses albuminoides pendant la grossesse chez le cobaye," *Compt. Rend. Soc. Biol.*, vol. lxi., 1907.

The placenta contains glycogen in amounts which vary greatly in different species.[3] It is found only in traces in Ruminants, but in great amount in Rodents (see Chapter X., p. 460). It occurs also at the margin of the zonary placenta in Carnivores, and in the human placenta. In many species it has not yet been investigated.

In the fœtus, the feature of the glycogen is not its high percentage, but its almost universal distribution in the developing tissues.[4] It has been shown by Bohr that the energy in the mammalian fœtus is supplied by the combustion of carbohydrates (see p. 553), and by the wide distribution of glycogen an available supply is procured in every part of the fœtal body in which the work of organisation is proceeding.

(*c*.) *The Daily Requirement of Carbohydrate for the Fœtus.*—Some idea can be obtained of the daily requirements of glycogen for the fœtus of the rabbit in the second half of pregnancy. The appended table, from the paper of Lochhead and Cramer,[5] gives the amount of glycogen contained in the unborn young from the eighteenth day of gestation till the day before parturition.

The table shows that 1·2 gm. of glycogen are deposited between the eighteenth and the twenty-eighth day, or about 0·2 gm. per fœtus. Hence the average daily deposition is 0·02 gm. per fœtus. In the later stages the rate of deposition increases out of proportion. This is due to the assumption of its glycogenic function by the fœtal liver.

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[1] Charrin and Guillemont, "Physiologie pathologique de la Grossesse," *Compt. Rend. Soc. Biol.*, 1899.

[2] Harding, "Nausea and Vomiting in Pregnancy," *The Lancet*, vol. ccl., 1921.

[3] Lochhead and Cramer, "The Glycogenic Changes in the Placenta and the Fœtus of the Pregnant Rabbit," *Proc. Roy. Soc. London*, B., vol. lxxx., 1908.

[4] Gierke, "Glycogen in der Morphologie des Zellstoffwechsels," *Habilitationsschrift*, Freiburg, 1905.

[5] Lochhead and Cramer, "The Glycogenic Changes in the Placenta and the Fœtus of the Pregnant Rabbit," *Proc. Roy. Soc. London*, Ser. B., vol. lxxx., 1908.

Day of Gestation.	Average Weight of each Fœtus in Grammes.	Average Amount of Glycogen per Fœtus.	Number of Fœtuses.	Total Amount of Glycogen.
18	0·89	·0018	8	·0144
20	2·32	·0050	6	·0300
21	3·28	·0080	5	·0400
22	4·13	·0103	4	·0412
23	7·20	·0203	8	·1624
24	9·75	·0346	6	·2076
25	20·23	·0808	7	·5656
26	11·24	·0257	5	·1285
27	32·84	·1418	3	·4254
28	32·07	·2017	6	1·2102
29	26·67	·1199	9	1·0791

TABLE to show the fœtal weight and amount of fœtal glycogen in the second half of pregnancy (rabbit). In the animal killed at the twenty-sixth day, the pregnancy was abnormal, one fœtus being dead and the others badly developed. In the last also the fœtuses were unusually small.

The amount of carbohydrate oxidised each day can be calculated from Bohr's figures. The oxygen consumption for a fœtus weighing 30 gm. is 0·14 c.c. per minute. This is sufficient to oxidise 0·00017 gm. of sugar, or 0·245 gm. per day, which is equal to 0·227 gm. of glycogen. Hence for six fœtuses, the average number, 1·362 gm. are required for combustion each day. In addition, an average of 0·3 gm. of glycogen is deposited in them daily near the end of pregnancy. Hence the total daily requirement for the unborn young at this stage is 1·662 gm. of glycogen. A small additional amount of carbohydrate is required for the daily increasing blood-serum, for the liquor amnii in the rabbit, and for the manufacture of mucin and other glycoproteins.

(*d.*) *Excretion of Carbohydrates in Pregnancy: Glycosuria and Lactosuria.*—Blot[1] was the first to postulate the occurrence of a "physiological glycosuria" in pregnancy. Kirsten[2] found sugar in the urine in the majority of cases of pregnancy and labour, and regularly in the puerperium. Hofmeister[3] first discussed the relationship of the glycosuria to milk secretion, and proved that the sugar excreted in the puerperium was lactose.[4] The sugar is in extremely small amounts, but above the normal. Lemaire[5] found

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[1] Blot, "De la glycosurie physiologique chez les femmes en couches, etc.," *Compt. Rend. Soc. Biol.*, vol. xliii., 1856.

[2] Kirsten, "Ueber das Vorkommen von Zucker im Harn der Schwangeren," *Monatsschr. f. Geburtsh. u. Frauenkrankh.*, vol. ix., 1857.

[3] Hofmeister, "Ueber Laktosurie," *Zeitsch. f. physiol. Chem.*, vol. i., 1877.

[4] Corroborated by Kaltenbach ("Die Laktosurie der Wöchnerinnen," *Zeitsch. f. Geburtsh. u. Gynäk.*, vol. iv.) and many others.

[5] Lemaire, "Ueber das Vorkommen von Milchzucker," *Zeitsch. f. physiol. Chem.*, vol. xxi., 1895.

0·003 to 0·009 per cent., and Brocard[1] an upper limit of 0·01 per cent. Zacharjewsky,[2] however, observed no increase in the reducing power of the urine on an ordinary diet during the last weeks of pregnancy. The first definite increase comes with the appearance of lactose in the urine after birth, though it may also be excreted a few days before birth. It is more evident when the milk is not utilised and becomes re-absorbed, but it rarely exceeds 0·3 per cent.[3] Extirpation of the mammary glands immediately stops the lactosuria,[4] and, if carried out in pregnancy, prevents it.[5] In 2200 consecutive cases Cron[6] found sixty-eight, or three per cent. of pregnant women whose urine gave a test for the presence of some reducing sugar; seventeen women gave a positive reaction during the puerperium. Cron points out that the presence of a reducing sugar during pregnancy or the puerperium is usually due to lactosuria or to alimentary glycosuria, and this condition must be distinguished from diabetes mellitus and other types of glycosuria. He estimates that 30·50 per cent. of pregnant women may at some time or another present an alimentary glycosuria.

Numerous observations[7] on the blood sugar during normal pregnancy fail to show any deviation from the normal in women. In rabbits Schirokauer[8] believes to have noted an increase; in two bitches Oppler and Rona[9] failed to find any difference before and after they had littered. During labour the blood sugar rises and falls again in the puerperium. Very high values were found in eclampsia if the blood was taken immediately after a convulsion. This suggests that the hyperglycæmia of labour is related to the increased activity of the muscles.

The glycosuria of pregnancy has been ascribed to a diminished glycolysis (Brocard) and to hepatic insufficiency (Cristalli),[1] without sufficient evidence. The greater tendency to alimentary glycosuria in pregnancy was upheld by Lanz,[2] who observed it after the administration of 100 gm. of glucose. It was confirmed by Payer,[3] Reichenstein,[4] and Bergsma.[5] In his observations on partially pancreatectomised dogs Allen[6] found a slight lowering of the limit of carbohydrate assimilation during pregnancy. These observations are difficult to interpret, because, as we shall see in dealing with the fat metabolism, the pregnant organism requires a larger amount of carbohydrate than the non-pregnant organism to keep the metabolism normal as judged by the tendency to the excretion of the acetone bodies.

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[1] Brocard, "La Glycosurie de la Grossesse," *Thèse de Paris*, 1898.

[2] Zacharjewsky, *loc. cit.*, *Zeitsch. f. Biol.*, vol. xxx., 1894.

[3] The inability of the organism to oxidise lactose was demonstrated by Voit ("Verhalten der Zuckerarten im menschlichen Organismus," *Deut. Arch. f. klin. Med.*, vol. lviii., 1897).

[4] Sinéty, "Urine of Guinea-Pigs in Puerperium," *Compt. Rend. Soc. Biol.*, vol. l.

[5] V. Noorden, *loc. cit.*, vol. i. (see also pp. 602-605).

[6] Cron, "Glycosuria during Pregnancy," *Amer. Jour. Obst. and Gynæc.*, vol. i., 1920.

[7] Benthin, "Der Blutzuckergehalt in der Schwangerschaft, in der Geburt, im Wochenbett und bei Eklampsie," *Zeitsch. f. Geburtsh. u. Gynäk.*, vol. lxix., 1911. Neubauer and Novack, "Zur Frage der Adrenalinaemie und des Blutzuckers in der Schwangerschaft," *Deutsche med. Woch.*, 1911. Bergsma, "Der Zuckerstoffwechsel in der Schwangerschaft," *Zeitsch. f. Geburtsh. u. Gynäk.*, vol. lxxii., 1912. Ryser, "Blutzucker während der Schwangerschaft," *Deutsch. Arch. f. klin. Med.*, 1916.

[8] Schirokauer, "Zum Zuckerstoffwechsel in der Schwangerschaft," *Berl. klin. Woch.*, 1912.

[9] Oppler and Rona, "Untersuchungen über den Blutzucker," *Biochem. Zeitsch.*, vol. xiii., 1908.

E. *The Metabolism of Fats in Pregnancy*

(*a.*) *The Absorption of Fats by the Mother.*—The absorption of fats from the intestine is increased during pregnancy (Ferroni[7]), the neutral fats, fatty acids, cholesterin, and soaps contained in the fæces being all decreased towards the end of the gestation period. This is the time when the subcutaneous tissues of the fœtus receive an abundant supply. They rapidly reach the normal level in the puerperium. There is a corresponding increase of fat in the maternal blood in the dog and guinea-pig, and the excess disappears after parturition (Capaldi).[8]

(*b.*) *Fats of the Maternal Organism.*—According to Miotti,[9] the liver cells contain a continuously increasing amount of fat, first in the central parts of the lobule and later throughout. He looks on it as a fatty infiltration, and concludes that an increased fat formation takes places during pregnancy. This observation has been confirmed by Mottram,[10] who compares it to the fatty infiltration of the liver which occurs in hunger. This "physiological" infiltration is due to a mobilisation of fat from the depots. It passes first to the liver where it is desaturated and then passes on to the tissues.

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[1] Cristalli, *Ricerche sulla presenza dello zuchero nelle orine delle donne gravide e puerpere*, Naples, 1900.

[2] Lanz, "Ueber alimentäre Glykosurie bei Graviden," *Wien. med. Presse*, 1895.

[3] Payer, "Einfluss des Zuckers auf den Stoffwechsel der Schwangeren," *Monatsschr. f. Geburtsh. u. Gynäk.*, vol. x., 1899.

[4] Reichenstein, "Glycosurie und Schwangerschaft," *Wiener klin. Wochenschr.*, 1909; *ibid.*, 1911.

[5] Bergsma, *loc. cit.*

[6] Allen, "The Influence of Pregnancy upon Experimental Diabetes," *Amer. Jour. Physiol.*, vol. liv., 1920.

[7] Ferroni, "I grassi neutri . . . delle gravide e delle puerpere sane," *Ann. di Ost. e Ginec.*, 1905.

[8] Capaldi, "Sul contenuto di grasso del sangue nella gravidanza e nel puerperio," *di Ann. Ost. e Ginec.*, 1905.

[9] Miotti, "Contributo allo studio istologico de fegato durante la gravidanza," *Ann. di Ost. e Ginec*, 1900.

[10] Mottram and Coope, "Fatty Acid Infiltration of the Liver during Pregnancy and Lactation," *Jour. Physiol.*, vol. xlix., 1914.

A very significant change in the metabolism of fats—using the term fat here to include lipoids—is the great increase in cholesterin and cholesterinesters in the blood during pregnancy. There is also an increase in the true fats (glycerinesters) but not in the phosphorised fats (lecithin). This was first recognised by Herrmann and Neumann[1] and has been confirmed by many workers. There is an associated increase in the storage of these substances in the corpora lutea and in the adrenal cortex. The blood of the fœtus contains always less cholesterin than the maternal blood and does not contain any cholesterinesters at all. The hyper-cholesterinæmia of the mother diminishes towards the end of pregnancy and with the beginning of lactation: there is an outpouring of these substances in the milk. It is found accordingly that the hypercholesterinæmia passes off more quickly in mothers who suckle their children than in those who do not. The bile of the mother is also richer in cholesterin, and according to M'Nee[2] this may account for the more frequent occurrence of gall-stones in women. The function of cholesterin is not definitely known, although there is no lack of speculation concerning it. The meaning of this hypercholesterinæmia of pregnancy is therefore not yet understood.

In the placenta there is evidence of a transmission of fat to the product of conception. Even in the early stages of pregnancy the cells of the uterine mucosa are infiltrated with fat, and the trophoblast is pervaded with fat globules. In Ungulates a large amount of fat is contained in the uterine milk (see p. 435). In those mammalian orders in which the trophoblast is directly bathed by maternal blood, the fat dissolved in it forms a second available supply. There is no reason to doubt an active transference of fat from the mother, or to assume that a transformation from carbohydrates or proteins is necessary.

(c.) *The Daily Requirement of Fat for the Fœtus.*—The daily requirement of fat varies very considerably during pregnancy, and especially towards the end, when the subcutaneous fat of the fœtus is deposited. Fehling[3] found 0·5 per cent. of fat in the human fœtus at the fourth month, over four per cent. at the eighth, and nine per cent. at the ninth month. In guinea-pigs the fœtal liver contains considerable amounts of fat, especially towards the end of gestation.[1] This excess of fat, which is less saturated than connective tissue fat, disappears during the first two or three days after birth.

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[1] Herrmann and Neumann, "Über die Lipoide der Gravidität, etc.," *Wiener klin. Wochenschrift*, vol. xxv., 1912.

[2] M'Nee, "Cholesterin: An Account of its Relations to Pathology and Physiology," *Quar. Jour. Medicine*, vol. vii., 1914. This paper contains a complete bibliography up to 1914.

[3] Fehling, "Beiträge zur Physiologie des placentaren Stoffverkehrs," *Arch. f. Gynäk.*, vol. xi., 1877.

(*d.*) *Origin of the Fœtal Fat.*—As to its origin, Thiemich[2] states that it is not derived from the alimentary fat of the mother, since after feeding a dog in two successive pregnancies on widely different fats, palmin and linseed oil, he could determine no difference in the constitution of the fœtal fat. Oshima[3] comes to the same conclusion from his investigations on the number of ultra-microscopic particles in the blood of cats, rabbits, and guinea-pigs. He states that the number is dependent on the stage of development, and independent of the condition of the mother's blood—for example, when a great increase is produced by rich fat-feeding. Capaldi, on the other hand, states that the percentage of fat is the same in the maternal and fœtal blood, at least at the end of pregnancy. Some feeding experiments carried out by Hofbauer[4] agree with this. He administered coco-nut oil, which consists essentially of the triglycerides of laurinic and myristinic acids with a very small quantity of tripalmitin, to three pregnant guinea-pigs, and demonstrated laurinic acid in considerable amount in the fœtuses. Hence the fat of the food, or at least one of its fatty acids, had been transmitted across the placenta. But any conclusions based on the introduction of a foreign fat must be guarded.

In the fœtus, fat is present in many of the tissues in a state of fine division. Its widespread distribution and its amount, probably equal at least to that of glycogen, are a characteristic of fœtal life; but its significance is not obvious if, as Bohr states, it is not a source of energy. Guillot[5] showed that it did become a source of energy immediately after birth, when the fœtus is faced suddenly with the necessity to maintain its body temperature against a lower external temperature. The rapid disappearance of fat from the fœtal liver, observed by Imrie immediately after birth, also suggests such an explanation, although Imrie himself suggests that the fat in the fœtal liver is destined for the connective tissue depots. He found twelve per cent. of fat in the lungs of fœtuses dying during labour, and only six per cent. after several hours' respiration. Fat may have anabolic functions to perform in the building up of the fœtal body, *e.g.* in the synthesis of lecithin.

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[1] Imrie and Graham, "The Fat Content of Embryonic Livers," *Jour. Biol. Chem.*, vol. xliv., 1920.

[2] Thiemich, "Ueber die Herkunft des fötalen Fettes," *Centralbl. f. Phys.*, vol. xii., 1898.

[3] Oshima, "Ueber das Vorkommen von ultra-mikroscopischen Teilchen im fötalen Blute," *Centralbl. f. Phys.*, vol. xxi., 1907.

[4] Hofbauer, *Biologie der menschlichen Plazenta*, Wien and Leipzig, 1905.

[5] Guillot, quoted in Richet's *Dictionnaire de Physiologie*, Article "Fœtus."

(*c.*) *Disturbances of Fat Metabolism in Pregnancy. The Excretion of the Acetone Bodies.*—The "acetone bodies"—aceto-acetic acid and β-oxybutyric acid—are intermediate products of the oxidation of the fatty acids. Acetone is formed from them by further decomposition. They are formed normally, and very small amounts are excreted in the urine of normal persons, while the bulk is further oxidised to CO_2 and H_2O. Vicarelli[1] was the first to observe the presence of these bodies in the urine of pregnant women. He attributed it to the presence of a dead fœtus, a conclusion which was disproved by Menu and Mercier,[2] who found it to be present when the fœtus was living, but when the pregnancy was abnormal in other respects (albuminuria, eclampsia). Stolz,[3] and later Bar,[4] found acetone also in a number of normal pregnancies. In order to appreciate the findings and conclusions of the older observers it is necessary to remember that the tests they had at their disposal were not very delicate and gave positive results only when considerable amounts were present. A second factor of importance in interpreting their findings is the diet. In the normal organism the appearance of the acetone bodies in the urine is related to the diet, in the sense that the excretion is greatly increased when carbohydrates are withheld from the diet, and also of course when no food at all is taken. This is supposed to be due to a greatly increased formation of these substances when the liver has lost its glycogen and has to draw upon fats and protein for the formation of carbohydrate. According to some authorities it is due to a deficient oxidation which allows these substances to escape in the urine before they are burnt up. Porges and Novack[5] made the important observation that in normal pregnant women the acetone bodies can always be made to appear in the urine by keeping them for one day on a special diet which does not lead to an increased excretion in normal non-pregnant women. This diet was poor in carbohydrates but by no means carbohydrate free. Conversely they could suppress the excretion of these substances by adding carbohydrate to the diet. With a more delicate test for the acetone bodies (Rothera's test) Harding[6] has recently confirmed these results. He makes the interesting suggestion that the nausea and vomiting of early pregnancy is related to this abnormal metabolic condition and can be combated by an abundant supply of carbohydrates given at frequent intervals. It is certainly suggestive that the "morning sickness" occurs at that time of the day when there has been the longest interval after a meal. This tendency of the normal pregnant organism to acetonuria suggests further that at least some forms of the pernicious vomiting of pregnancy, where large amounts of the acetone bodies are excreted, are merely an aggravation, due to some toxic factor, of this normal tendency. For we know from the occurrence of the acetonuria following after chloroform or ether narcosis or in some febrile conditions that some toxins are capable of inducing this metabolic disturbance.

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[1] Vicarelli, "Die Acetonurie während der Schwangerschaft," *Prager med. Wochenschr.*, 1893.

[2] Menu and Mercier, *Bulletin de la Soc. d'Obstétrique de Paris*, 1898.

[3] Stolz, "Die Acetonurie in der Schwangerschaft, Geburt und im Wochenbett," *Arch. f. Gyn.*, vol. lxv., 1902.

[4] Bar, *Leçons de Pathologie Obstétricale*, p. 822, 1907.

[5] Porges and Novack, "Über die Ursache der Acetonurie bei Schwangeren," *Berl. klin. Woch.*, vol. xlviii., ii., 1911.

[6] Harding, *loc. cit.*

The work of Bohr and of Lochhead and Cramer has shown the importance of carbohydrates for the development of the fœtus, in Rodents at any rate. The facts referred to in this section indicate that this holds good also for the human fœtus. Pregnancy in the human subject imposes such a drain of carbohydrate material from the mother that for the maintenance of a normal metabolism a larger supply of carbohydrate is necessary for the pregnant than for the non-pregnant woman.

The formation of these acid bodies in pregnancy naturally leads to a discussion of the acid-base equilibrium in pregnancy.

F. *The Acid-base Equilibrium in Pregnancy. The so-called "Acidosis of Pregnancy"*

The question to be discussed here is whether the acid-base equilibrium is disturbed in normal pregnancy by the excessive formation of acid metabolites. The body tends to maintain at a constant level the reaction of the blood or, as it is called, the hydrogen-ion concentration of the blood. It can compensate for an increased formation of acid bodies chiefly by the following three methods: firstly, by an increased lung ventilation which leads to a lowering of the alveolar CO_2 pressure; secondly, by a transformation of the disodium phosphate excreted in the urine into the acid monosodium phosphate; and thirdly, by combining acid with ammonia, which would usually be converted into urea, and excreting the ammonium salt in the urine. The criteria of an increased formation of acid metabolites—a condition which is now usually designated by the term "acidosis"—are therefore lowering of the alveolar CO_2, the acidity of the urine, and the increased excretion of ammonia. These three factors do not necessarily come into play simultaneously. It should be also borne in mind that the conception of "acidosis" as defined by these criteria is rather different from the conception of acidosis as used by the older writers, who applied it to conditions where abnormal acids such as aceto-acetic acid and oxybutyric acid can be definitely identified, as, for instance, in the acidosis of diabetes or of pernicious vomiting of pregnancy (see above, p. 544). In this latter condition there is, as has been shown above, a greatly increased excretion of ammonia in the urine for which, no doubt, the factor of starvation is largely responsible, while the alveolar CO_2 shows only a comparatively slight diminution, as Loosee and van Slyke[1] point out. In normal pregnancies the observations of Hasselbalch and Gammeltoft[2] have shown that there is a slight but distinct fall in the alveolar CO_2 pressure. This fall was observed in one case very early in pregnancy, namely on the first occasion when menstruation ceased, and gradually progressed to 30 mm. against a normal value varying between 35 mm. and 43 mm. In another case the alveolar CO_2 pressure before birth was 32 mm. and rose to a mean value of 38 mm. after birth.

Hasselbalch also holds that the ammonia excretion is slightly increased in pregnancy, although as Murlin has pointed out (see above, p. 534) the argument as to the existence of an acidosis from the increased ammonia excretion is open to criticism.

There is also a distinct diminution in the CO_2 combining power of the blood: the so-called "alkali reserve" of the blood. Thus Slemons[3] found in normal pregnancies values of 37 c.c. to 50 c.c. CO_2 per 100 c.c. of plasma against values from 55 c.c. to 75 c.c. for normal non-pregnant women. The toxæmias of pregnancy show the same apparent paradox with reference to the alkali reserve as they do with the alveolar CO_2: the diminution of the alkali reserve in these conditions is no greater than in normal pregnancies, while the ammonia index gives very high figures.

If we accept the definition of acidosis as an increased formation of acid metabolites as evidenced by a fall in the alveolar CO_2 pressure, then pregnancy is accompanied by an acidosis. This "acidosis" does not, however, affect the reaction of the blood, which is stated to be normal. It is not yet clear how this acidosis is related to the acidosis of the pernicious vomiting of pregnancy, in which the main alteration of the acid-base equilibrium is an increased excretion of ammonia with only a slight change in the alveolar CO_2 pressure. The "acidosis" of normal pregnancy, which leads to an increased lung ventilation, may be a physiological method by which the maternal organism adapts itself to the presence of the fœtus with its increased demand for oxygen and its increased formation of CO_2.

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[1] Loosee and van Slyke, "The Toxæmias of Pregnancy," *Amer. Jour. Med. Sciences*, vol. cliii., 1917.

[2] Hasselbalch and Gammeltoft, "Neutralitätsregulation des graviden Organismus," *Biochem. Zeitsch.*, vol. lxviii., 1915; *ibid.*, vol. lxxiv., 1916.

[3] Slemons, "Analysis of the Blood in Eclampsia and Allied Conditions," *Amer. Jour. Obstet.*, vol. lxxvii., 1918. See also Emge, "Acidosis in Normal Uterine Pregnancies," *Amer. Jour. Obstet.*, vol. lxxiv., 1916; vol. lxxvii., 1918.

G. *The Metabolism of Metals and Salts in Pregnancy*

Little is known regarding the metabolism of the individual metals and salts. The fixation of mineral elements is slight at the beginning, but becomes active towards the end of pregnancy. From first to last, about a hundred grammes are transferred from the mother to the human fœtus. With a few exceptions, the mineral salts are approximately in the same proportion throughout pregnancy. The exceptions are sodium, potassium, and calcium, of which sodium decreases and calcium increases with the replacement of cartilage by bone, and potassium increases with the increased manufacture of red blood corpuscles (Hugounenq[1]).

The analyses of Camerer and Söldener[2] of the ash of the human fœtus have given the following results:—

P_2O_5	CaO	Na_2O	K_2O	MgO	Fe_2O_3	Cl
38·5	36·1	9·1	7·8	0·9	0·8	7·7

The significance of these figures lies in the preponderance of CaO and P_2O_5 in the ash. The analyses of Michel[3] and of Fehling[4] of embryos at different stages of development show that the retention of mineral salts by the fœtus does not proceed evenly. There is a sudden increase, beginning in the twenty-ninth week, in the retention of calcium from 0·4 gm. to 2 gm. and of phosphorus from 0·3 gm. to 1·3 gm. These relations have been expressed very clearly in graphs by Hoffström.[5] The relatively high retention of iron is also significant.

(*a*.) *Iron.*—Part at least of the iron for the fœtus is derived from the hæmoglobin of the maternal organism. In the poly-cotyledonary placenta of Ruminants and the zonary placenta of Carnivores, the disintegration of red blood corpuscles has been demonstrated. There is less certainty regarding the actual ingestion of the red cells by the syncytium of the discoid placenta, though it has been described by

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[1] Hugounenq, "Recherches sur la statique des éléments minéraux et particulièrement du fer chez le fœtus humain," *Compt. Rend. Soc. Biol.*, 11th series, vol. i., 1889.

[2] Camerer and Söldener, "Die chemische Zusammensetzung des neugeborenen Menschen," *Zeitsch. f. Biol.*, vol. xxv., 1902.

[3] Michel, "Sur la composition de l'embrion et du fœtus humain aux différents époques de la grossesse," *Compt. Rend. de la Soc. de Biol.*, vol. li., 1899.

[4] Fehling, "Beiträge zur Phys. des placentaren Stoffverkehrs," *Zeitsch. f. Gynäkol.*, vol. ii.

[5] Hoffström, *loc. cit.*

Peters in an early human ovum.[1] But in all placentæ yet investigated, iron-containing granules have been observed in the trophoblast. The possible sources are hæmoglobin, which is in part absorbed as such by the trophoblast in man (Bonnet[2]), nucleoprotein, and the reserve iron of the mother. Nuclein is the only iron-containing constituent of yolk of egg, and must serve for the manufacture of hæmoglobin in the developing chick. It is also known that in the adult organism nucleoprotein is a better source of iron for hæmoglobin than any inorganic or other organic compound hitherto administered by the mouth.[3] Hence it is not difficult to conceive that the same process may occur in the fœtus. But whether it is the food nucleoproteins or the organised nuclein bodies of the maternal organism that are utilised, is unknown.[4] With regard to the reserve iron of the mother, it is stated by Charrin[5] that the store in the spleen is reduced during pregnancy.

In the fœtus iron is required for the synthesis of hæmoglobin (see p. 505) and nucleoproteins.[6] But large amounts of iron are also stored in the liver and other organs of the embryo without being used immediately. According to Bunge's[7] law, this forms a reserve which is drawn on after birth to make up for the deficiency of the iron in the milk. Thus the liver of a rabbit contains 18 mg. of iron per 100 gm. body-weight at birth, and only 3·2 mg. twenty-four days later. This fact is of great practical importance in the nutrition of infants. The period during which milk is an adequate diet for the infant is limited by the reserve of iron which the infant has stored away in its body before birth. This reserve is sufficient to last during the normal period of lactation. Then a mixed diet, containing food richer in iron than milk, is required. If the mother during pregnancy is kept on a diet rich in iron, the embryo will store more iron than when the diet is poor in iron. If the supply of iron to the mother is kept low during repeated pregnancies abortion may occur.[8]

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[1] See Chapter X., p. 505.

[2] *Ibid.*

[3] V. Noorden, *loc. cit.*, vol. i., p. 78.

[4] As the purine bases of the urine are stated to be decreased in pregnancy, the maternal nucleins are probably not a source of iron for the fœtus to any appreciable extent.

[5] Charrin, "Physiologie pathologique de la grossesse," *Compt. Rend. Soc. de Biol.*, 1899.

[6] The nucleoproteins of the fœtal placenta in the sheep differ in their chemical constitution from those of the maternal placenta. They are probably synthesised in the ovum from lower complexes, in the same way as the nucleoproteins of the chick embryo are built up though the egg contains no purine bases.

[7] Bunge, "Weitere Untersuchungen über die Aufnahme des Eisens in den Organismus des Säuglings," *Zeitsch. f. physiol. Chem.*, vols. xvi. and xvii., 1892-93.

[8] Fetzer, "Experimentelle Untersuchungen über den Eisenstoffwechsel," 26 *Kongress f. inn. Medizin*, 1909.

According to Veit and Scholten,[1] the villi can dissolve intact red cells of the circulating blood, just as the solution of erythrocytes can be produced by placental extracts. As a result of this, hæmoglobinæmia may occur in pregnancy. Wychgel[2] observed it in eight out of twenty-three pregnancies, and the condition occurs more frequently still in eclampsia. At present, however, it is not yet generally accepted that an erythrotoxin is formed by the syncytium, though Bonnet[3] has shown histologically that a destruction of red cells probably takes place during life. He noticed on the surface of the villi "perfect and damaged erythrocytes in all stages of degeneration, clumping and solution." So Hofbauer found, by adding neutral-red to the chorionic villi of two fresh two-months' placentæ teased in saline, that many of the blood corpuscles showed red dots indicating degeneration.

(*b.*) *Calcium.*—The great demand for calcium by the developing embryo, especially during the last three months of pregnancy, would lead one to suppose that pregnancy involves a loss of calcium on the part of the mother. It has, in fact, been stated that teeth are apt to become brittle in pregnancy from a decrease in calcium fluoride and a deficiency in enamel formation.[4] Evidence of a special drain on calcium is also found in puerperal osteomalacia, which occurs in poor people who presumably live on an ill-constructed diet, and which has been produced experimentally as the result of such a diet in animals.[5] The effect on the teeth is not admitted as a general occurrence in pregnancy by some authorities,[6] if it occurs at all, and is probably the result of a diet deficient in calcium. The exact observations of Hoffström have shown clearly that on a suitable calcium-rich diet the mother actually gains in calcium. On such a diet Hoffström's patient retained 34·3 gm. Ca during the whole pregnancy, of which 30·1 gm. were required by the fœtus, so that the mother ended her pregnancy with a net gain of 4·2 gm. Ca. As has been stated, the requirements of the fœtus are particularly high during the last three months of pregnancy, and the mother responds to this increased call for calcium by diminishing the excretion of calcium in the urine and to a lesser extent by the intestine. Even on this diet and with a total positive balance there are short periods of a loss of calcium. This occurred particularly at the end of the sixth month (thirtieth week) when there was a sudden increase in the fœtal requirements of Ca. It is necessary to emphasise a point in Hoffström's observations, the importance of which has not been sufficiently recognised, namely the nature of the diet on which Hoffström's patient lived. She was allowed a free choice of food and from a sample menu given in Hoffström's paper it is clear that the diet was particularly rich in calcium. She consumed a litre of milk a day in addition to other calcium-rich foods and the result is an average weekly intake of Ca of 1·7 gm. throughout the whole of pregnancy. Tigerstedt calculates that the amount of Ca necessary to maintain a normal non-pregnant organism does not exceed 1 gm. Ca per week. When the diet is poor in calcium, as in the experiments of Dibbelt[1] on a pregnant bitch, the embryos do not suffer a loss of calcium. The deficiency is made up entirely by the maternal tissues, which in Dibbelt's experiments had to furnish 4·2 gm. Ca. The calcium content of the blood is said to be increased during pregnancy.[2] These considerations emphasise the importance of including in the dietary of pregnant women food material rich in calcium such as milk, butter, cheese, green vegetables, certain fruits such as oranges, lemons, etc. With reference to this point it is important to note that margarine is practically free from calcium, while butter is a food particularly rich in calcium.

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[1] Veit and Scholten, "Synzytiolyse und Hämolyse," *Zeitsch. f. Geburtsh. u. Gynäk.*, vol. xlix.

[2] Wychgel, "Untersuchungen über das Pigment der Haut und der Urin während der Schwangerschaft," *Zeitsch. f. Geburtsh. u. Gynäk.*, vol. xlvii.

[3] Bonnet, quoted by Hofbauer (*Biologie der menschlichen Plazenta*, Wien und Leipzig, 1905).

[4] Terrier, "De l'influence de la grossesse sur les dents," *Thèse de Paris*, 1899.

[5] Stilling and Mering, "Ueber experimentelle Erzeugung von Osteomalacie," *Zentralbl. f. med. Wissenschaft*, 1889.

[6] Dr. Sim Wallace, Private communication.

(*c.*) *Magnesium.*—The magnesium intake and output was also observed by Hoffström. The amounts which came into question are much smaller and the results are irregular. On the whole there is a magnesium retention amounting on an average to 0·013 gm. per day with an average daily intake of 0·282 gm. which Hoffström considers to be low. There are periods of magnesium loss. But even with this low intake Hoffström's case retained during the whole of pregnancy a total of 2·44 gm., of which 0·98 gm. was fixed by the fœtus, so that the maternal organism gained.

(*d.*) *Phosphorus.*—The phosphorus metabolism runs as a rule parallel to the nitrogen metabolism. The same has been observed in pregnancy (V. Eeke,[3] Schrader[4]). Jagerroos,[5] however, showed an equilibrium between intake and output of phosphorus in a pregnant dog which showed a distinct loss of nitrogen. But since such abnormalities have also been observed in normal persons (Ehrström[1]) it cannot be considered as being peculiar to pregnancy. In Hoffström's case[2] there was an increased phosphorus retention, which was associated with a diminished excretion of phosphates in the urine and resembled in that respect the progressive nitrogen retention. But the nitrogen was retained somewhat more actively than the phosphorus, so that there was no strict parallelism. Altogether 56 gm. of phosphorus were retained during pregnancy, of which 18 gm. were fixed by the fœtus, so that the maternal organism showed a net gain of 38 gm. Similar results have been obtained by Bar[3] and by Landsberg.[4]

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[1] Dibbelt, "Die Bedeutung der Kalksalze f. d. Schwangerschaft und Stillperiode, etc.," *Ziegler's Beitr. path. Anat.*, vol. xlviii., 1910.

[2] Lamers, "Der Kalkgehalt des menschlichen Blutes, etc.," *Zeitsch. f. Geburtsh. u. Gynäk.*, vol. lxxi., 1912.

[3] Ver Eeke, *loc. cit.*

[4] Schrader, "Stoffwechsel während der Schwangerschaft," *Arch. f. Gynäk.*, vol. lx., 1900.

[5] Jagerroos, *loc. cit.*

(*e.*) *Sulphur.*—Hoffström's observations are, as he himself states, not conclusive, because the analyses for the sulphur intake were vitiated by an error. His analyses of the excreted sulphur show a progressive diminution of the total sulphur which is due entirely to a diminution of the so-called "oxidised sulphur," the sulphur excreted in the various kinds of sulphates. The so-called "neutral sulphur," which is derived mainly from cystin and from the taurin of the bile, showed actually an increase. The relative proportion of neutral sulphur to oxidised sulphur, which is supposed to be about 1 : 5 in a normal person, was in Hoffström's cases completely changed and was 1 : 2. Bar found a much higher excretion of total sulphur with a relation of neutral sulphur to oxidised sulphur of 1 : 9. Landsberg has been able to demonstrate a sulphur retention during the end of pregnancy which was proportionate to the nitrogen retention. Hoffström interprets the diminution of the oxidised sulphur in his case as indicating a diminished store of bases in the body, while the increase in the neutral, *i.e.* unoxidised sulphur, he interprets as being due to a diminished power of oxidation on the part of the pregnant organism. Murlin, however, has pointed out that this change in the sulphur excretion can be explained as being the result of the progressive sulphur retention, just as in the case of nitrogen.

(*f.*) *Chlorides.*—The first estimations of the chlorides of the urine in pregnancy indicated no variation from the non-pregnant level (Winckel[5]). Repeated investigations have been carried out since the discovery that a retention of chlorides may occur in nephritis and lead to œdema (Widal[6]).

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[1] Ehrström, "Zur Kenntniss des Phosphorumsatzes bei dem erwachsenen Menschen," *Skandin. Arch. f. Physiol.*, vol. xiv., 1903.

[2] Hoffström, *loc. cit.*

[3] Bar, *loc. cit.*

[4] Landsberg, *loc. cit.*

[5] Winckel, *Studien über Stoffwechsel etc.*, Rostock, 1865.

[6] Widal, "La cure de déchloruration dans le mal de Bright," *Arch. Génér.*, vol. cxciii., 1904.

Biancardi[1] stated that œdemas in pregnancy were sometimes due to the same cause, and might be cured by decreasing the chlorides of the food. Next Cramer[2] affirmed that all cases of hydrops graviditatis without albuminuria were due to a retention of sodium chloride; and Boni, whose careful investigations of the urine in pregnancy have already been referred to, found that the chlorine excretion was decreased, and remained low during the puerperium. Along with this there is a retention of water to maintain osmotic balance. Normally 90 to 100 per cent. of the water taken in is excreted in the urine, but the percentage fell to 72 per cent. in a primipara, 53 per cent. in a multipara, and 48 per cent. in a twin pregnancy (Slemons[3]). Such a retention did not occur in a woman who was later delivered of dead twins, 93 per cent. of the water being excreted in the urine.

Birnbaum's[4] results are not in agreement with the others. He states that a retention of chlorides occurs only in the nephritis of pregnancy, and not in normal pregnancy or in hydrops without albuminuria. In the blood-serum the chlorides were 0·1740 per cent. and 0·1775 per cent. in two cases, and 0·1733 per cent. in a non-pregnant woman.

H. *Respiratory Exchange and Energy Metabolism during Pregnancy*

Modifications in the respiratory exchange arise from the alterations in the maternal organism, and from the requirements of the product of conception. To a certain extent diffusion of oxygen takes place from mother to fœtus, as it has been proved, by experiments in asphyxia of the mother, that the direction in which oxygen goes across the placenta depends on the tension. Whether there is also a gas-secretion by the trophoblast is unknown.

With regard to the fœtus, Pflüger argued on theoretical grounds that the oxidation processes were inconsiderable, and the oxygen intake small. Experimentally Cohnstein and N. Zuntz[5] arrived at a similar conclusion. More recently, however, Bohr[6] has shown that in the later stages of pregnancy the fœtal guinea-pig has a respiratory exchange at least as high as the mother. The actual figures per kilo per hour which he obtained were 462 c.c. CO_2 for the mother and 509 c.c. CO_2 for the fœtus. The difference between these figures is within the rather high limits of error in such a complicated experiment. He has also shown that the fœtal respiratory quotient is unity, indicating that carbohydrates are the source of energy. The same has been found in new-born puppies before suckling (Murlin[1]). Russell and Gye[2] determined the oxygen consumption of embryonic mouse tissue by suspending the minced tissue in blood and analysing the blood in Barcroft's apparatus. They found values much lower than those obtained for normal adult tissues under the same conditions. Their results are therefore more in accord with Pflüger's conception. Russell and Woglom[3] in subsequent observations determined the respiratory quotient of minced embryonic tissue (skin) and found it to be unity. It is well to remember that all these experiments refer only to the fœtus in the later stages of development, and that they entirely leave out of account the placental metabolism. In the later stages there is a wide distribution of glycogen throughout the tissues of the fœtus, and the fœtal liver has assumed its glycogenic function. It is scarcely justifiable to extend Bohr's results to the early stages of pregnancy, when the placenta probably takes a leading part in embryonic development. It may be that at that time also glycogen is the source of energy for the placenta in Rodents, but it cannot be so in Ruminants. In their placentæ glycogen is found only in traces, while fat is in considerable amount. Hence we must not assume that in Ruminants the energy is derived from the combustion of carbohydrates until experimental evidence has been obtained.

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[1] Biancardi, "Sulla cura declorurante nelle nefriti e nelle albuminurie nel campo ostetrico," *Ann. di Ost. e Ginec.*, 1905.

[2] Cramer, "Chlornatrium-Entziehung bei Hydrops Graviditatis," *Monatsschrift f. Geburtsh. u. Gynäk.*, vol. xxiii.

[3] Slemons, "Metabolism during Pregnancy, Labour, and Puerperium," *Johns Hopkins Hosp. Rep.*, vol. xii., 1904.

[4] Birnbaum, "Excretion of Chlorides during Pregnancy," *Arch. f. Gynäk.*, vol. lxxxiii., 1907.

[5] Cohnstein and Zuntz, "Untersuchungen über das Blut, den Kreislauf, und die Atmung beim Säugetierfötus," *Pflüger's Arch.*, vol. xxxiv., 1884.

[6] Bohr, "Der Respiratorische Stoffwechsel des Säugetierembryos," *Skandin. Arch. f. Physiol.*, vol. x., 1900.

With regard to the total energy exchange the older investigations of Oddi and Vicarelli[4] showed a progressive increase in the consumption of oxygen during the last third of pregnancy in rats; but Magnus-Levy raises the objection that the movements of the animals were not restricted. The observations of Magnus-Levy,[5] F. Müller,[6] and L. Zuntz[7] showed that in the human pregnancy there was certainly no decrease in metabolism, the metabolic changes being at least as active in the fœtus as in the mother.

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[1] Murlin, "Protein Metabolism in Development," *Amer. Jour. of Physiol.*, vol. xxiii., 1908-09.

[2] Russell and Gye, "The Oxygen Consumption of Mouse Tissue," *British Jour. Exp. Pathol.*, vol. i., 1920.

[3] Russell and Woglom, "The Respiratory Exchange of Surviving Mouse Tissues, etc.," *ibid.*, vol. i., 1920.

[4] Oddi and Vicarelli, "Influence de la grossesse sur l'échange respiratoire," *Arch. ital. de Biol.*, vol. xv., 1891.

[5] Magnus-Levy, "Stoffwechsel und Nährungsbedarf in der Schwangerschaft," Vortrag, *Zeitsch. f. Geburtsh. u. Gynäk.*, vol. lii., 1904; also v. Noorden, *loc. cit.*, vol. i.

[6] F. Müller, "Diskussion zum Vortrag von Magnus-Levy," see v. Noorden, *loc. cit.*, vol. i.

[7] Zuntz (L.), "Der Stoffaustausch zwischen Mutter und Frucht," *Ergebn. d. Phys.*, 1908.

L. Zuntz's[1] more recent and extended observations on women before and during pregnancy showed a distinct increase in the energy metabolism, which became progressively greater towards the end of pregnancy. At the same time he observed, from the middle of pregnancy on, as Magnus-Levy had before him, an increased lung ventilation. This fact is of interest as it indicates a stimulation of the respiratory centre by acid metabolites, in other words, it is an expression of an acidosis (see p. 545). The increased muscular work involved in this increased lung ventilation accounts for at least part of the higher values obtained for the gaseous exchange. If a corresponding amount is deducted there still remains a slight increase in the gaseous metabolism which is on the whole proportional to the increase in weight. In one case there was an increase out of proportion to the increase in weight. Carpenter and Murlin[2] have made very complete observations on pregnant women during the last few days of pregnancy in a respiration calorimeter. Unfortunately they could not obtain observations on the same individuals in the non-pregnant state and were therefore restricted to comparing their results on pregnant women with observations on eight other normal women. They found an increase in the energy exchange which was four per cent. higher than could be accounted for by the increase in weight. Their measurements gave an energy requirement for the resting pregnant woman during the end of pregnancy of 24 cal. per day and per kilo. This must be regarded as a minimum value. Hoffström's case had an intake of 31 cal. per day per kilo.

In a dog pregnant with one puppy Murlin[3] found a very marked increase in the total energy production amounting to nine per cent. which became apparent in the sixth week and persisted till the end of pregnancy (ninth week). The same dog became pregnant again with five puppies. The increase then was much greater and was exactly proportional to the greater weight of the offspring. In comparing these results with those obtained in women the greater weight of the puppy embryos in proportion to that of the mother must be borne in mind.

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[1] Zuntz (L.), "Respiratorische Stoffwechsel u. Atmung während der Gravidität," *Arch. f. Gynäkol.*, vol. xc., 1910.

[2] Carpenter and Murlin, "The Energy Metabolism of Mother and Child just before and just after Birth," *Arch. of Int. Med.*, vol. vii., 1911.

[3] Murlin, "Energy Metabolism of the Pregnant Dog," *Amer. Jour. Physiol.*, vol. xxvi., 1910.

I. *Summary of Changes in the Metabolism of Pregnancy*

The maternal organism adapts itself to the progressively increasing requirements of the fœtus, which dominate the metabolism of the mother. Under suitable dietary conditions this adaptation is so successful that the maternal organism completes pregnancy with a gain. The dietary conditions which must be observed more particularly are an abundant supply of firstly carbohydrates, secondly calcium, and thirdly vitamins. The gain at the end of pregnancy is a reserve for the mother to draw upon during the puerperium and lactation. Under unsuitable dietary conditions the mother suffers first.

The adaptation of the maternal organism involves changes in the metabolism of the mother, of which the most definitely established is the occurrence of an acidosis due probably to the slightly increased formation of aceto-acetic acid and oxybutyric acids. Under normal conditions this acidosis remains within physiological limits and, like the acidosis which sets in as the result of exposure to high altitudes, it subserves the function of increasing the ventilation of the lungs. Many facts point to the maternal liver as the organ on which pregnancy imposes a special strain and this is confirmed by a hypertrophy of this organ occurring in pregnancy.[1] But no clear evidence has yet been brought that normal pregnancy involves a hepatic insufficiency.

K. *Analogy between the Metabolism of Pregnant Animals and Tumour-Bearing Animals*

Certain changes in the maternal organism, for instance those due to the changes in the mamma and uterus, are obviously specific to pregnancy. Others, however, are apparently simply the result of the presence of a mass of rapidly growing cells in an adult organism. For as Cramer[2] has pointed out, the metabolism of tumour-bearing animals presents a close similarity to that of pregnant animals. There is in both cases an increased nitrogen retention[3] which is in excess of that necessary for the mass of growing cells and thus benefits the organism serving as a host. There is the same faculty in both cancerous cells and embryonic cells of being able to build up living protoplasm with less nitrogen than the non-growing or more slowly growing cells of the adult host. There is an increased demand for carbohydrates which suggests that carbohydrate material is essential for growth.[1] There is further the hypertrophy of the liver which has been observed in tumour-bearing animals[2] as in pregnant animals.[3] This close analogy suggests that perhaps the physiological acidosis of pregnancy may occur in cancer, and that the diminished CO_2 pressure in the alveolar air, which is such a very early indication of this acidosis in pregnancy, might also be found comparatively early in cancer.

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[1] Herring, "The Effect of Pregnancy upon the Size and Weight of some of the Organs of the Body," *Brit. Med. Jour.*, 11th December 1920.

[2] Cramer, "Zur Biochemie des Wachstums," *VIII. Internat. Physiologen Kongress*, Vienna, 1910. Also *III. Sci. Report*, Imperial Cancer Research Fund, 1908.

[3] Cramer and Pringle, "Contributions to the Biochemistry of Growth," *Proc. Roy. Soc.*, B., vol. lxxxii., 1910; vol. lxxxvi., 1912.

III. The Changes in the Maternal Tissues during Pregnancy

The changes in the ovaries, the mammæ, and the mucous membrane of the uterus are dealt with elsewhere. To the changes in some of the other organs, a brief consideration is here given.

(*a.*) *The Blood.*—Ehrlich's[4] statement that pregnancy does not appreciably alter the number of the red blood corpuscles has been more or less firmly established by Ingerslev,[5] Dubner,[6] Bernhard[7] and others in man, by Spiegelberg and Gscheidlen[8] in the dog, and by Cohnstein[9] in the sheep. Their investigations have upset the older theory of a hydræmia of pregnancy.

There is evidence of a slight increase of hæmoglobin (Payer,[10] Fehling,[11] Winckelmann,[12] Wild[13]), especially towards the end of pregnancy.

The number of leucocytes increases during pregnancy, and there is a further rise during the act of parturition (Nasse,[14] Lebedeff,[15] Rieder[16]). The leucocytosis is referred by some to the lymphoid tissue of the endometrium, and by others to an increase in the groups of lymphatic glands in the neighbourhood of the genital apparatus. The spleen is not obviously affected, but a remarkable change was observed in rats in the thymus. It was reduced to half its normal size and histologically presented the appearances of involution. These findings confirm the view expressed above that the functional activity of the lymphoid tissue is of special importance during the period of pregnancy.

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[1] Cramer and Lochhead, "Contributions to the Biochemistry of Growth," *Proc. Roy. Soc.*, vol. lxxxvi., 1913.

[2] Medigreceanu, "Ueber die Grösseverhältnisse einiger der wichtigsten Organe bei Tumortragenden Ratten u. Mäusen," *Berl. klin. Wochenschrift*, 1910.

[3] Herring, *loc. cit.*

[4] Ehrlich, "Die Anämien," in Nothnagel's *Spezielle Pathologie.*

[5] Ingerslev, "Ueber die Menge der roten Blutkörperchen bei Schwangeren," *Centralbl. f. Gynäk.*, 1879.

[6] Dubner, "Untersuchungen über den Hämoglobingehalt des Blutes, etc.," *Münch. med. Woch.*, 1890.

[7] Bernhard, "Untersuchungen über Hämoglobingehalt und Blutkörperchenzahl in der letzten Zeit der Schwangerschaft," *Münch. med. Woch.*, 1892.

[8] Spiegelberg and Gscheidlen, "Untersuchungen über die Blutmenge trächtiger Hunde," *Arch. f. Geburtsh. u. Gynäk.*, vol. iv.

[9] Cohnstein, "Blutveränderungen während der Schwangerschaft," *Pflüger's Arch.*, vol. xxxiv., 1884.

[10] Payer, *vide* v. Winckel's *Handbuch der Geburtshülfe*, vol. i., H. 1.

[11] Fehling, "Ueber Blutbeschaffenheit, etc.," *Arch. f. Gynäk.*, vol. xxviii., 1886.

[12] Winckelmann, "Hämoglobin-Bestimmungen bei Schwangeren und Wöchnerinnen," *Inaug. Diss.*, Heidelberg, 1888.

[13] Wild, "Untersuchungen über den Hämoglobingehalt und die Anzahl der roten und weissen Blutkörperchen bei Schwangeren," *Arch. f. Gynäk.*, vol. liii.

[14] Nasse, *Das Blut*, Bonn, 1836.

[15] Lebedeff, quoted in v. Winckel's *Handbuch der Geburtshülfe*, vol. i., H. 1.

[16] Rieder, *Beiträge zur Kenntnis der Leukocytose und verwandter Zustande des Blutes*, Leipzig, 1892.

According to Spiegelberg and Gscheidlen, the total amount of blood is increased during pregnancy in the dog from 7·8 per cent. to 9 per cent. of the body-weight. There is no essential difference in the specific gravity (Nasse, Blumreich[1]). The reaction of the blood has been dealt with above (see p. 546).

(*b*.) *The Heart and Circulation.*—Older authorities stated that a true hypertrophy of the heart occurred during pregnancy, and was caused by the increased length and size of the uterine vessels, the placental circulation, and the compression of the aorta by the gravid uterus. Experiments showed, however, that the uterine vessels did not offer a resistance which required an increase in the work of the heart (Engström[2]), while the compression of the abdominal aorta and the introduction of large quantities of fluid into the abdominal cavity produced no change which could be detected from the pulse (Heinricius[3]). The controversy has been a long one, but it does not properly belong to this article. In the rat Herring[4] failed to find a hypertrophy or enlargement as the result of pregnancy.

It has been suggested that the increased work of the heart is due to an increased peripheral resistance from the presence of a vaso-constricting substance in the blood. Whether such a substance exists is very doubtful. The investigation of extracts of the placenta by Lochhead and Cramer[5] in 1907, proved that this organ contained no blood-pressure raising substance. The substances extracted by Dixon and Taylor[6] from the placenta and observed to have an adrenalin-like action, were subsequently shown to arise in the course of putrefaction.

The blood-pressure is not affected in normal pregnancy, but is always raised in labour as a result of the uterine contractions. After parturition the pressure falls, but rises again on the third day of the puerperium.

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[1] Blumreich, "Der Einfluss der Gravidität auf die Blutalkalescenz," *Arch. f. Gynäk.*, vol. lix., 1899.

[2] Engström, "L'Influence de la grossesse sur la circulation," *Arch. de Gyn.*, vol. ii., 1886.

[3] Heinricius, *Experimentelle und klinische Untersuchungen über Circulationsverhalten der Mutter und der Frucht*, Helsingfors, 1889.

[4] Herring, "The Effect of Pregnancy, etc.," *British Med. Jour.*, 11th December 1920.

[5] Lochhead and Cramer, Unpublished observations.

[6] Dixon and Taylor, "On the Physiological Action of the Placenta," *Proc. Roy. Soc. Med.*, London, vol. i., 1908.

The effects of pregnancy in the human female on the heart have been the subject of a recent monograph,[1] to which the reader is referred for details. So far as the normal heart is concerned the effects may be summarised as follows: There is no change in the circulation during the first months of pregnancy. After the sixth month the response to effort is restricted: breathlessness appears after an effort which can be accomplished in comfort by a normal non-pregnant woman. There is no hypertrophy of the left ventricle. Owing to the displacement of the abdominal viscera the shape of the chest is altered, so that there is a displacement of the heart. The apex beat may be pushed out one inch beyond the left nipple line, and this has led to the erroneous supposition of the occurrence of a hypertrophy. Similarly an increased area of dullness to the right of the sternum can usually be made out.[2] This also is due to the abnormal position of the heart, and is not to be interpreted as a dilatation of the right ventricle. There is venous stasis, probably due to pressure on the pelvic veins, and a tendency to dropsy, the cause of which is not clear.

Varices of the lower extremities and external genitals are frequent in human pregnancy. They are due mainly to the increased intra-abdominal pressure and the stretching of the abdominal wall. Secondary thromboses are common in the puerperium.

(*c.*) *The Ductless Glands.*—There is regularly a swelling of the thyroid gland in pregnancy (Tait[3]), which consists of a simple hypertrophy, and not a vascular engorgement or cystic change (Freund[4]). It has been shown experimentally in cats that a remnant of the gland, which is sufficient to maintain health in the non-pregnant state, is insufficient after the onset of pregnancy (Lange[5]). Herring's[6] observations on pregnant rats show no increase in size and no histological changes indicating an increase of secretion. The adrenals, however, showed a slight increase in weight and the load of adrenalin was slightly higher. The hypercholesterinæmia of pregnancy seems to suggest that there are probably functional changes in the adrenal cortex. The pituitary body of pregnant rats is diminished in size by about twenty-four per cent. This diminution affects mainly the glandular lobe, which shows a great diminution of the granular eosinophil cells. The human pituitary is stated to be enlarged in pregnancy, and the eosinophil cells of the glandular lobe are then replaced by large neutrophil cells.[1]

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[1] Mackenzie (Sir J.), *Heart Disease and Pregnancy*, London, 1921.

[2] v. Winckel, *Handbuch der Geburtshülfe*, vol. i.

[3] Tait, "Enlargement of the Thyroid Body in Pregnancy," *Obstet. Jour.*, 1875.

[4] Freund, "Ueber die Beziehung der Schilddrüse, etc.," *Deuts. Zeitsch. f. Chir.*, vol. xxxi., 1890.

[5] Lange, "Die Beziehungen der Schilddrüse zur Schwangerschaft," *Zeitsch. f. Geburtsh. u. Gynäk.*, vol. xl., 1899.

[6] Herring, *loc. cit.*

(*d.*) *The Skin.*—The cause of the increased pigmentation of the skin in pregnancy is little understood. It has been looked on as a simple deposit of pigment, as the result of infection with the *Microsporon furfur*, the cause of pityriasis versicolor which not infrequently attacks pregnant women, and as a subcutaneous hæmorrhage.[2] Jeannin[3] first suggested that it was derived from hæmoglobin set free by the solution of red blood corpuscles. According to Veit[4] the hæmolysis may be produced by the circulation of syncytial elements in the blood. The presence of iron in the pigment, though strongly denied by Truzzi,[5] has recently been demonstrated by Wychgel.[6] He associates its presence with the frequent occurrence of hæmoglobinuria in pregnancy. V. Fürth and Schneider's suggestion that the pigment is derived from tyrosin by the action of a placental tyrosinase is mentioned elsewhere (Chapter X., p. 507).

An abnormal development of the hair of the face and body is occasionally seen in pregnancy (Slocum,[7] Halban[8]). Under the name of *dermographismus*, Freund[9] describes a phenomenon, often met with in pregnancy, similar to the *tache cérébrale* of meningitis and other nervous affections. It may be elicited even in the early stages of gestation, and is best shown by stroking the skin over the sternum or fundus uteri.

(*e.*) *The Mammæ.*—The growth of the mammary glands is brought about by the development of new vesicles, the widening of existing blood-channels, and the formation of new vessels.[10] Even in the first half of pregnancy, and sometimes in the first weeks, the mammæ contain colostrum, a milky fluid composed of proteins, albumen, globulin, and casein, the carbohydrate lactose, fat, free fatty acids, lecithin, cholesterin, free glycero-phosphoric acid, and urea (Winterstein and Stickler[11]).

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[1] Erdheim and Stumme, *Über die Schwangerschaftsveränderung der Hypophyse.* Ziegler, *Beitr. z. pathol. Anat.*, vol. xlvi., 1909.

[2] See v. Winckel's *Handbuch der Geburtshülfe*, vol. i., H. 1.

[3] Jeannin, "Observations pour servir à l'histoire du masque des femmes enceintes," *Gaz. Hebdom.*, 1868.

[4] Veit and Scholten, "Synzytiolyse und Hämolyse," *Zeitsch. f. Geburtsh. u. Gynäk.*, vol. xlix., 1903.

[5] Truzzi, "Ueber die Genese der Hyperchromie der Haut in der Gravidität," *Monatsschr. f. Geburtsh.*, vol. xi., 1898.

[6] Wychgel, "Untersuchungen über das Pigment der Haut und den Urin während der Schwangerschaft," *Zeitsch. f. Geburtsh. u. Gynäk.*, vol. xlvii.

[7] Slocum, "Hair Development in Pregnancy," *New York Med. Rec.*, 1875.

[8] Halban, "Zur Frage der Graviditätshypertrichose," *Wien. klin. Woch.*, 1907.

[9] Freund, "Die Haut bei Schwangeren," *Verhandl. d.* VI. *deutsch. Dermatologen-Kongr. zu Strassburg.*

[10] See Chapter XIII.

[11] Winterstein and Stickler, "Die chemische Zusammensetzung des Colostrums," *Zeitsch. f. physiol. Chem.*, vol. xlvii., 1906.

CHAPTER XII

THE INNERVATION OF THE FEMALE GENERATIVE ORGANS—UTERINE CONTRACTION—PARTURITION—THE PUERPERAL STATE

> "Birth is the end of that time when we really knew our business, and the beginning of the days wherein we know not what we would do, or do."—SAMUEL BUTLER.

THE innervation of the generative organs of the male was dealt with at some length in an earlier part of this work. It remains in the present chapter to describe the nerve supply to the female generative system, and more particularly to the uterus, since this is the organ which is especially concerned in the process of parturition. But before giving an account of the innervation of the internal organs, the nerve supply to the vulva and clitoris may be briefly dealt with.

THE INNERVATION OF THE EXTERNAL GENERATIVE ORGANS

The external generative organs in the female are similarly innervated to those of the male (p. 265 *et seq.*).

Langley and Anderson[1] found that stimulation of the first five lumbar nerves in the cat, or the third, fourth, and fifth lumbar nerves in the rabbit, produced the same effects as in the male excepting that they were less pronounced. The effects were (1) Pallor of the clitoris and of the mucous membrane of the vulva, accompanied by slight retraction of the clitoris, (2) Contraction of the vulva, and (3) Contraction of the muscles of the adjoining skin, drawing the vulva dorsally towards the rectum.

Langley,[2] and subsequently Langley and Anderson,[3] found that two groups of effects, which were antagonistic to one another, could be produced by stimulating the sacral set of nerves in the vertebral canal, but that, as in the male, only those fibres which exercised an inhibitory influence run from the spinal cord in the sacral nerve roots. The inhibitory effects produced were (1) Flushing of the vulva and clitoris, (2) Dilatation of the vulva, and (3) Relaxation of the skin muscles surrounding the vulva. The visceral motor effects were the same as those produced by the lumbar set of nerves as described above. Besides these effects, contraction was induced in the external sphincter of the vagina and in the striated genital muscles.

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[1] Langley and Anderson, "The Innervation of the Pelvic and Adjoining Viscera," *Jour. of Physiol.*, vol. xix., 1895.

[2] Langley, "The Innervation of the Pelvic Viscera," *Proc. Phys. Soc., Jour. of Physiol.*, vol. xii., 1891.

[3] Langley and Anderson, *loc. cit.*

The Innervation of the Ovaries

The ovary is innervated from the sympathetic plexus accompanying the ovarian artery and from the plexus associated with the ovarian branch of the uterine artery. It is generally supposed that the nerve fibres, which are non-medullated, are merely vascular in function.[1] The fact that ovulation in some animals only occurs as a consequence of coition, and then takes place at a definite time afterwards, points to the conclusion that the follicles discharge in response to a stimulus conveyed to the ovary by its nerves (see p. 129). It has been suggested that the rupture is due to the stimulation of erectile tissue.[2] Nerve fibres have been described in the tissue immediately surrounding the follicles, and have even been traced as far as the follicular epithelium.

The Innervation of the Uterus and Vagina and the Mechanism of Uterine Contraction

It is well known that the onset of parturition is manifested by rhythmically repeated contractions of the uterus which constitute the "labour pains." But although the contractions are most pronounced at this period, observations on animals have shown that even in a virgin uterus rhythmical movements may occur.

Kehrer[3] showed long ago that a uterus separated from the body is capable of undergoing contractions if kept moist, and at the normal body temperature. More recently Helme,[4] Kurdinowski,[5]

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[1] Von Herff, "Ueber den feineren Verlauf der Nerven im Eierstöcke des Menschens," *Zeitsch. f. Geburt. u. Gynäk.*, vol. xxiv., 1892. Gawronsky, "Ueber Verbreitung und Endigungen der Nerven in den weiblichen Genitalien," *Arch. f. Gynäk.*, vol. xlvii., 1894. Kallius, "Nervendigungen in Drüsen d. Eierstöcke," Merkel and Bonnet's *Ergeb. d. Anat. u. Entwick.*, vol. iv., 1895. Mandl, "Ueber Anordnung und Endigungsweise der Nerven im Ovarium," *Arch. f. Gynäk.*, vol. xlviii., 1894-95. Vallet, "Nerfs d'Ovarie, etc.," *Thesis*, Paris, 1900. Abel and McIlroy, "Nerves of the Ovary," *Phys. Soc.*, 5th June 1909. See also references on p. 358.

[2] Rouget, "Recherches sur les Organes Érectiles de la Femme," *Jour. de la Phys.*, vol. i., 1858.

[3] Kehrer, "Zusammenziehungen der glatten Genitalmuskelatur, etc.," *Beiträge zur Vergl. u. Exper. Geburtskunde*, 1867.

[4] Helme, "Contributions to the Physiology of the Uterus and the Physiological Action of Drugs upon it," *Reports of the Laboratory of the Royal College of Physicians*, Edinburgh, vol. iii., 1891.

[5] Kurdinowski, "Physiologische und pharmakologische Versuche an der isolirten Gebärmutter," *Arch. f. Anat. u. Phys.*, Phys. Abth. (supplement), 1904.

Franz,[1] and others have confirmed Kehrer's observation, thus proving that the movements are not dependent on impulses received from the central nervous system. Those investigators showed that the excised uterus may undergo regular contractions for a prolonged period if placed in a warm bath of normal saline solution or on having its vessels perfused with Locke's solution. According to Franz the excised virgin uterus exhibits no spontaneous contractions, but Helme and Kurdinowski state that they may occur, but that they are much weaker than those taking place during and after pregnancy.

The movements of the uterus have lately been more fully investigated by Cushny,[2] who has carried out a large number of experiments upon rabbits and other animals. This author states that in virgins the unexcised uterus may remain motionless for a long time, but that after manipulation or exposure to air rhythmic contractions are often developed. He is disposed to believe, therefore, that the virgin uterus in the intact animal undergoes no spontaneous movements. In animals in a state of "heat," and during and after pregnancy, spontaneous contractions could generally be discerned from the first, and the author is doubtful if the organ ever resumes its original inert condition after it has once been pregnant. In some cases the movements seemed to occur almost simultaneously throughout the entire organ, but in others the circular muscle fibres contracted independently of the longitudinal, and *vice versa*. Mechanical or electrical stimulation caused very powerful contractions, but these were elicited more easily in the pregnant than in the virgin uterus, while the increased irritability was found to persist after pregnancy was over.

Helme stated that a shutting off of the blood-supply in the excised and perfused uterus of the sheep brought about contraction. Kurdinowski, on the other hand, found that in the intact animal the opposite effect was produced. Cushny's experiments for the most part confirm those of Kurdinowski, but clamping the aorta in the cat led to conflicting results, since in two cases it was succeeded by relaxation and in three by contraction. No reason could be assigned for this divergence.

It has long been known that uterine contractions can be induced by nervous stimulation.[3] Thus Serres[4] showed that irritation of the spinal cord in the lumbar region excited the uterus to contract, and later investigators have obtained similar results.[1] Röhrig[2] showed that asphyxia which may bring about uterine contractions (and abortion in the pregnant condition) cannot do so if the lumbar cord is destroyed. Frankenhauser[3] and Körner[4] discovered that the efferent nerve fibres left the lumbar region of the spinal cord, and after traversing the sympathetic, the inferior mesenteric ganglia and the aortic plexus, made their way to the uterus. Langley[5] found that the majority passed to this organ by way of the sympathetic in the region of the fourth, fifth, and sixth lumbar ganglia, so that they probably arise from the third, fourth, and fifth spinal nerves. Subsequently Langley and Anderson[6] showed that stimulation of the second, third, fourth, and fifth lumbar nerves (in cats and rabbits) causes pallor and contraction of the Fallopian tubes, uterus, or vagina, but that stimulation of the first and sixth lumbar nerves produces no effect. They state that the efferent fibres are motor for the muscular walls and vaso-constrictor for the small arteries. The effect on the uterus and vagina was found to vary with the state of the uterus in regard to parturition. Langley and Anderson state that the sacral nerves send neither motor nor inhibitory fibres to any of the internal generative organs, thus differing from Kehrer, Körner, and others, who say that they obtained contraction of the uterus on stimulating these nerves.

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[1] Franz, "Studien zur Physiologie des Uterus," *Zeitsch. f. Geburt. u. Gynäk.*, vol. liii., 1904.

[2] Cushny, "On the Movements of the Uterus," *Jour. of Physiol.*, vol. xxxv., 1906.

[3] Feldman (*The Principles of Ante-Natal and Post-Natal Child Physiology*, London, 1920) states that there are probably centres for uterine contraction in the cortex, medulla, and cerebellum, since stimulation of these areas causes uterine contractions, but he does not cite his authorities.

[4] Serres, *Anatomie Comparée du Cerveau*, 1824.

Keiffer[7] also independently investigated the innervation of the uterus, and the results obtained by exciting various nerves, his observations agreeing for the most part with those of Langley and Anderson.[8]

Cushny, in the paper already referred to, has described at some length the effects of hypogastric stimulation, which produced in the rabbit powerful contraction of the whole uterus irrespective of its condition in regard to the occurrence of pregnancy. If the stimulation was prolonged for more than fifteen seconds the organ remained in a state of extreme contraction (*tetanus uteri*), but oscillations soon began again and a gradual relaxation followed. Cushny shows also that the hypogastric contains inhibitory fibres, and in one exceptional case (a pregnant rabbit) stimulation of this nerve induced pure inhibition, the uterus ceasing to contract at all. Moreover, in the virgin cat the effect of hypogastric stimulation was inhibitory, the organ undergoing relaxation. On the other hand, in the cat during pregnancy, or as a general rule after pregnancy, hypogastric stimulation led to strong and immediate contraction just as in the rabbit. It is supposed, therefore, that the inhibitory fibres prevail in the virgin, but that during and after pregnancy the action of the motor fibres conceals their presence.[1]

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[1] Budge, "Ueber das Centrum genitospinale des Nervus sympatheticus," *Virchow's Archiv*, vol. xv., 1858. Riemann, "Einige Bemerkungen über die Innervation der Gebärmutter," *Arch. f. Gynäk.*, vol. ii., 1871.

[2] Röhrig, "Experimentelle Untersuchungen über die Physiologie der Uterusbewegung," *Virchow's Archiv*, vol. lxxvi., 1879.

[3] Frankenhauser, "Die Bewegungsnerven der Gebärmutter," *Jenaische Zeitsch. f. Med.*, vol. i., 1864.

[4] Körner, *Studien d. Phys. Instituts zu Breslau*, 1865.

[5] Langley, *loc. cit.*

[6] Langley and Anderson, *loc. cit.*

[7] Keiffer, *Recherches sur la Physiologie de l'Utérus*, Bruxelles, 1896.

[8] Feldman (*loc. cit.*) states that motor nerve fibres to the uterus come from the pneumogastric, phrenic, and splanchnic, and that sensory fibres pass through the sacral nerves.

Fellner[2] states that the "nervi erigentes" are motor for the longitudinal muscles of the uterus and for the circular muscles of the cervix, but are inhibitory for the circular muscles of the uterus and the longitudinal muscles of the cervix. According to the same author the hypogastric nerves are motor for the circular muscles of the corpus uteri and for the longitudinal muscles of the cervix, but are inhibitory for the longitudinal muscles of the uterus and for the circular muscles of the cervix.

Dembo[3] has described a peripheral nerve centre for the uterus in the upper part of the anterior wall of the vagina in the rabbit. Stimulation of this cêntre produced a very distinct contraction of both uterine cornua.

According to Jacob[4] there is an inhibitory centre for uterine contraction situated in the medulla oblongata. This assertion is based on experiments upon rabbits, in which it was found that stimulation of the medulla caused the movements of the uterus to cease. Moreover, it is to some extent borne out by the fact that the "pains" of labour can often be inhibited by emotions and other contemporary actions of the central nervous system (see below, p. 572).

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[1] Cushny deals also with the action of various drugs on the uterus, and for an account of this subject the reader is referred to his paper (*loc. cit.*). See also Dale, "On some Physiological Actions of Ergot," *Jour. of Physiol.*, vol. xxxiv., 1906. The effects of temperature upon uterine contraction were first described by Runge (M.) ("Die Wirkung hoher und niedriger Temperaturen auf den Uterus," *Arch. f. Gynäk.*, vol. xiii., 1878), who found that hot water caused increased contraction followed by paralysis, while cold water produced tetanus. Helme (*loc. cit.*) obtained results which were mostly similar. Kurdinowski also found that cold excited contraction to tetanus, and that long-continued mechanical stimulation produced exhaustion. Asphyxia did not cause contraction, and experimental anæmia had no effect.

[2] Fellner, "Ueber die Bewegungen und Hemmungsnerven des Uterus," *Arch. f. Gynäk.*, vol. lxxx., 1906. Labhardt ("Das Verhalten der Nerven in der Substanz des Uterus," *Arch. f. Gynäk.*, vol. lxxx., 1906) describes an extensive system of nerves in the uterus of man and of the rabbit, the main trunks lying between the middle layer of muscles and giving off intrafascicular bundles. Keiffer (*Bull. Soc. d'Obstét.*, Paris, 1908, Nos. 2 and 3) describes sympathetic ganglia in the uterine and vaginal walls in the course of the large nerves coming from the hypogastric plexus.

[3] Dembo, "Zur Frage über die Unabhängigkeit der Kontraktinen der Gebärmutter von dem Cerebrospinalnervensystem," Abstract in *Biol. Centralbl.*, vol. iv., 1885. (The original is in Russian.)

[4] Jacob, "Ueber die Rhythmischen Bewegungen des Kaninchenuterus," *Verhandl. der Phys. Gesell. zu Berlin*, *Arch. f. Anat. u. Phys.*, Phys. Abth., 1884.

It is well known that uterine contraction can be induced by the presence of a foreign body in the uterus, by injections into the rectum, by the application of the child to the breast, and by various other means. According to Kurdinowski[1] the sensation of any violent pain may cause uterine contraction in animals, and the organ may respond to remote stimulation (*e.g.* in the ears). These observations alone are sufficient to show that the contraction is often a reflex act. The experimental evidence cited above shows no less clearly that the controlling centre is in the lumbar portion of the spinal cord. Nevertheless there are many indications, as just mentioned, that the movements of the uterus can be brought under the influence of a higher centre situated in the brain. On the other hand, the fact that rhythmical contractions can continue to occur in the absence of all nervous connections is a certain proof that they are primarily independent of the central nervous system, although normally they are to a large extent influenced by it. It must be concluded, therefore, that the power to contract and relax rhythmically is an inherent property of the uterus.

The question as to the nature of the mechanism involved in uterine contraction is inseparably connected with the further problem concerning the part played by nervous influence in controlling the course of parturition. This subject is dealt with below (p. 570).

THE NORMAL COURSE OF PARTURITION IN THE HUMAN FEMALE

The increased size of the fœtus, together with the accumulation of the amniotic fluid, causes the uterus towards the end of pregnancy to become considerably distended. The enlargement is still further increased by the growth of the uterine wall itself. Partly as a consequence of this enlargement the waves of contraction which were present at the beginning of pregnancy, or even previously, as above described, become much more marked, but are still unaccompanied by painful sensation. With the onset of labour, however, these unconscious painless contractions are replaced by others of increasing intensity, and in the human subject distinctly affecting consciousness and giving rise to severe suffering. These are the "labour pains" which bring about the dilatation of the cervix uteri and lead to the expulsion of the child followed by the placenta.

[1] Kurdinowski, "Ueber die Reflectorische Wechselbeziehung zwischen den Brüstdrüsen und dem Uterus," *Arch. f. Gynäk.*, vol. lxxxi., 1907.

At the commencement of labour the contractions do not occur oftener than once every half or quarter of an hour, but they soon become more frequent, and recur eventually at intervals of two or three minutes. Their average duration is about a minute, though actual pain is experienced for a shorter time.[1] Polaillon[2] and Schutz[3] have shown from tracings that the period of increase occupies the main portion of the "pain," its acme being of short duration. In animals possessing bi-cornuate uteri the contractions are said to be peristaltic in nature, but this is not so evident in the case of the human subject.

Williams[4] has discussed the question as to the amount of force exerted at each "pain" in a woman during delivery. He states that the expenditure of energy necessary to restrain the head of the child as it emerges from the vulva is represented by not more than fifty pounds, although the obstetrician sometimes finds it impossible to hold it back at the acme of the pain. Schutz[5] made an attempt to arrive at a more exact estimation by inserting into the uterus a rubber bag connected with a mercury manometer. He found that whereas the intra-uterine pressure between the contractions was represented by a column of mercury of 20 mm., during the pains it rose to a height of from 80 to 250 mm. This difference is calculated to represent a force of from 8½ to 27½ pounds.

The clinical course of labour and the muscular forces concerned in the process are fully dealt with in the text-books on Midwifery,[6] and it is not proposed in the present work to devote more than a very brief space to the consideration of this subject. It is customary to divide the period of labour into three stages.

The first stage is characterised by the dilatation of the cervix and os uteri. Galabin gives the following account of the mechanical processes which take place in the uterus during this stage of labour: "There are three elements in the mechanism of dilatation of the cervix and os; first, the mechanical stretching by the bag of membranes; secondly, the contraction of the longitudinal fibres of the uterus, which draw the cervix open; and thirdly, the physiological relaxation of the circular fibres, which [is always associated] with the contraction of the body of the uterus. It follows from the principles of mechanics that the effect of any given pressure within the bag of membranes in producing a tension of the edge, either of the internal or external os, is directly proportional to the diameter of the os, and therefore vanishes when the os is very small. Hence, if the os is closed to begin with, some dilatation by the stretching influence of the longitudinal fibres must have taken place before the mechanism of dilatation by the bag of membranes or parts of the fœtus can come into play. The mechanical action of the dilating part, as it is pressed into the cervix, is that of a wedge; a fluid and uniform wedge, in the case of the bag of membranes; a solid and irregular wedge, in the case of the head or other part of the fœtus. It follows that the effect produced by the wedge varies according to the acuteness of its angle at the points where it is in contact with the edge of the os. . . . It follows that the dilating force vanishes when there is no projection, and becomes greater the more complete is the projection. It follows also that it becomes progressively more and more effective in proportion to the degree of dilatation which has already been produced." [1]

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[1] Williams (W.), *Obstetrics*, London, 1904.

[2] Polaillon, *Recherches sur la Physiologie de l'Utérus Gravide*, Paris, 1880.

[3] Schutz, "Ueber die Formen der Wehenerven und über die Peristaltik des Menschlichen Uterus," *Arch. f. Gynäk.*, vol. xxvii., 1886.

[4] Williams, *loc. cit.*

[5] Schutz, "Ueber die Entwickelung der Kraft des Uterus in Verlaufe der Geburt," *Verhandl. d. Deutsch. Gesell. für Gynäk.*, 1895.

[6] See Williams, *loc. cit.* Galabin, *Manual of Midwifery*, 6th Edition, London, 1904, and the other text-books on the subject. See also Sellheim, "Die Physiologie der Weiblichen Geschlechtsorgane," Nagel's *Handbuch der Physiologie des Menschen*, vol. ii., Braunschweig, 1906.

The second stage, which has been called the expulsive stage, may be said to include the period from the complete dilatation of the os uteri to the delivery of the fœtus. When the os has become fully expanded, and the membranes have ruptured, there is generally a short lull in the pains of labour. At the end of the lull the contractions of the uterus begin to recur with increasing vigour and frequency, while the abdominal muscles which are brought into play for the first time exert on the uterus an additional extrinsic force similar to that exerted on the rectum during defæcation. These abdominal contractions are synchronous with those of the uterus, and therefore, like them, tend to occur rhythmically. At the commencement of the process the patient is able to some extent to control the contractions by an effort of the will, but later on they are quite involuntary. The combined effect of the contractions is to drive the child, usually head foremost, through the vagina and then out through the vulva, these, however, playing a purely passive part in the act of expulsion. Sometimes the membranes do not rupture before birth, and the child is born surrounded by a "caul."

The third stage of labour comprises the expulsion of the placenta. After the delivery of the child the uterus ceases to contract for a longer or shorter period, at the end of which its activity is renewed once more. At this time the placenta becomes completely separated from the wall of the uterus, and passes into the upper part of the vagina. It is expelled thence through the action of the muscles of the abdomen. During this stage there is almost invariably a certain amount of hæmorrhage, which is represented in normal cases by from three to four hundred cubic centimetres of blood.

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[1] Galabin, *loc. cit.*

The duration of labour shows considerable variation, but is generally longer in primiparous women (*i.e.* those who have never borne children before) than in multiparous ones. The average for the former is rather more than eighteen hours, the three stages respectively occupying sixteen, two, and from a quarter to half-an-hour. The average for multiparous women is twelve hours, eleven of which are occupied by the first, and one by the second stage. The duration of labour in primiparous women depends also upon age, being usually more prolonged in elderly subjects.

PARTURITION IN OTHER MAMMALIA

In animals the process of delivery varies somewhat in the different animals. In the horse the fœtus, which has been lying on its back during intra-uterine life, preparatory to birth changes on to its side and afterwards assumes the upright position, with its muzzle and forelegs in the direction of the pelvis. Dilatation of the passage follows, and the foal is delivered head first. In the cow and sheep the movements which occur are essentially similar. It is stated that the alteration in the position of the fœtus is not brought about by its own movements but by the uterine contractions. The revolution of the fœtus prior to birth in the mare and cow is apparently responsible for the torsion of the neck of the uterus which often occurs in these animals.

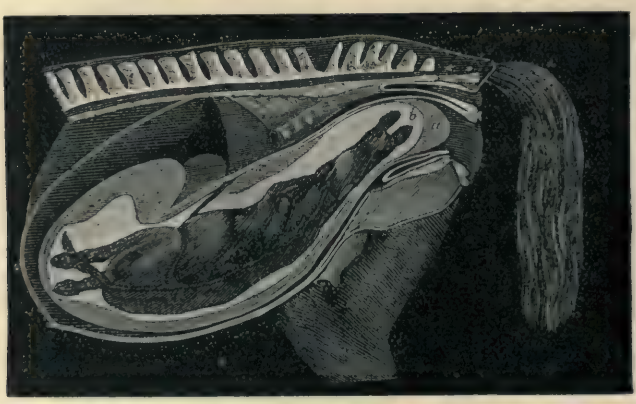

Fig. 158.—The first stage in the revolution of the equine fœtus. The os is dilated by the membranes, which have not yet ruptured. (After Franck. From Smith's *Veterinary Physiology*, Baillière, Tindall & Cox.)

Parturition in the mare is accompanied by a complete separation of the chorion from the uterine wall. As a consequence of this fact any difficulty experienced in delivery usually causes the death of the foal. In Ruminants, on the other hand, the separation of the cotyledons takes place very gradually, so that the connection between the maternal and fœtal circulation is maintained to some extent until the last. In these animals the process of parturition may last for hours (in the cow, about two hours; in the sheep, about fifteen minutes for each lamb born). In the mare, on the contrary, delivery is usually effected very rapidly[1] (five to fifteen minutes). In the sow, bitch, and cat it takes from ten to thirty minutes for each young one born, with sometimes an interval of an hour between the births. The fœtal membranes may be expelled with the young or be retained until a little later, when the uterus recovers its power and then expels them (in the mare several hours after the foal is born).

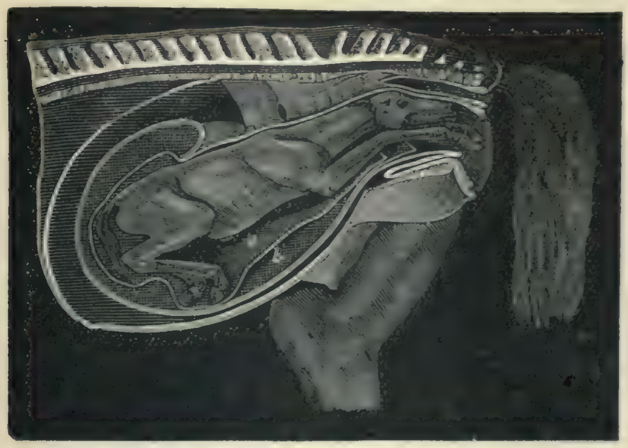

FIG. 159.—The foal in the normal position for delivery, the revolution being completed and the membranes ruptured. (After Franck. From Smith's *Veterinary Physiology*, Baillière, Tindall & Cox.)

In the Carnivora the mother usually gnaws through the umbilical cord but in the other animals it is torn.

In animals such as the rat, in which multiple conception is the rule, the "presentation" of the young at birth may be either "breech" or "head." The fœtuses tend to be expelled irregularly, some being discharged along with the placenta, while others are born separately.[1]

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[1] Smith (F.), *Veterinary Physiology*, 3rd Edition, London, 1907. Fleming, *Veterinary Obstetrics*, Craig's Edition, London, 1912. Wortley Axe, "The Mare and Foal," *Jour. Royal Agric. Soc.*, 3rd Series, vol. ix., 1898. Leeney, "The Lambing Pen," *Jour. Royal Agric. Soc.*, 3rd Series, vol. vii., 1896. Article on "Parturition" by the same author in *The Standard Cyclopedia of Modern Agriculture*, vol. ix., London, 1910.

Hartmann[2] has described the phenomena attending parturition in the opossum (*Didelphys virginiana*). The very immature young make their way unaided to the mother's pouch, and in so doing crawl three inches from the vagina over an entanglement of hair; amid a forest of hair the "ten-day-old fœtus" finds the nipple. Hartmann mentions that he found thirteen teats with eleven young attached.

In the actual process of being born the fœtuses of the opossum do not pass out through the lateral canals of the vagina, but break through a cleft-like rupture, the "pseudo-vaginal canal," into the median canal. This occurs also in *Dasyurus* and *Perameles*.[3]

The young kangaroo, like the opossum, reaches the pouch unaided.

THE NERVOUS MECHANISM OF PARTURITION

Parturition may be considered as being normally a reflex act, the centre of which is situated in the lumbar region of the spinal cord. On the other hand, it has been shown from experiments upon animals that the transmission of impulses through the cord is not absolutely essential to the occurrence of parturition.

Simpson (Sir James)[4] removed the spinal cord from the first dorsal vertebra downwards from a number of sows a few days before parturition was due. Some of the animals died as a result of the operation, but in others parturition proceeded normally, excepting that in each case the last fœtus of the series was not born. "The uterine contractions proceeding from fundus to cervix were sufficient to expel the fœtuses from the uterus; and each fœtus as it came into the vagina was thence extruded by the force transmitted from the fœtus behind it; but when the last fœtus came into the vagina it remained there, because there was nothing to transmit the uterine expulsive force, while the vaginal and abdominal muscles, being under the influence of the spinal nerves, had been rendered powerless by the removal of the spinal cord."

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[1] Brumpt, "Parturition chez le Rat blanc," *Bull. Soc. Zool. France*, vol. xxxii., 1907. The loosening of the placenta and other changes in *Tupaia* are described by van Herwerden, "Die puerperalen Vorgänge in der Mucosa uteri von *Tupaia javanica*," *Anat. Hefte*, vol. xxxii., 1907.

[2] Hartmann, "Studies in the Development of the Opossum, and the Phenomena of Parturition," *Anat. Record*, vol. xix., 1920.

[3] Hill, "On the Fœtal Membranes, Placentation, and Parturition of the Native Cat," *Anat. Anz.*, vol. xviii., 1900. See also *Proc. Linn. Soc. of N.S. Wales*, vols. xxiv. and xxv., 1899 and 1900. The lateral vaginal canals are described as enlarging in the prooestrum, containing a lymph-like fluid during œstrus when they are enormous and act as seminal reservoirs, since several days elapse between copulation and ovulation and subsequently becoming reduced.

[4] Simpson, *Selected Obstetric Works*, edited by W. H. Black, Edinburgh, 1871.

Riemann[1] states that after the destruction of the cord of a cat from the third dorsal vertebra downwards the animal gave birth to a kitten two days subsequently, shortly before its death.

Rein[2] describes experiments upon rabbits in which he severed the uterus from all nervous connection with the cerebrospinal system, and found afterwards that the mechanism of labour was not destroyed.

Furthermore, Oser and Schlesinger,[3] as a result of experimental evidence, state that parturition can occur in animals after the severance of the sympathetic nerves which pass to the uterus, but it is difficult to understand how this operation could have been made complete without interfering with the blood-supply to that organ.

More recently, Goltz and Ewald[4] have described an experiment in which they completely exsected the spinal cord of a bitch from the mid-dorsal region downwards, and found that after the operation the animal experienced normal "heat," became pregnant, and in due course produced a litter of pups. Kruiger and Offergeld[5] have also shown that parturition is possible after destruction of the cord. Goltz had already shown[6] that parturition could occur after the transection of the spinal cord in the dorsal region, and consequently after all connection with the higher centres had been cut off (see p. 514).

The last-mentioned fact is also demonstrated in the various cases in which parturition has proceeded normally in women suffering from paraplegia from the level of the mid-dorsal part of the spinal cord downwards. Routh[7] has recorded several such cases, and in all of them labour set in and proceeded regularly (or almost regularly), but without sensation. In Routh's own patient the injury was in the dorsal region of the cord, which was completely disorganised at the seat of the fracture of the spine, as the post-mortem evidence showed. In the lumbo-sacral region, however, there were a large number of cells which were normal in appearance, so that it could not be contended that the centre for parturition had been destroyed. Routh also refers to Brachet's case,[8] which he states is the only one recorded in which the spinal lesion was apparently in the lumbar region of the cord. In this case the uterus failed to make the normal contractions, and the child was eventually extracted with forceps. The placenta also had to be removed by hand. It is clear, therefore, that a spinal lesion in the lumbar region may result in materially weakening the action of the uterus, and so may hinder the normal course of labour. On the other hand, in those cases in which the lesion was in the dorsal part of the cord, the possibility of spinal reflexes in the lumbar region could not be excluded.[1]

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[1] Riemann, "Einige Bemerkungen über die Innervation der Gebärmutter," *Arch. f. Gynäk.*, vol. ii., 1871.

[2] Rein, "Beitrag zur Lehre von der Innervation des Uterus," *Pflüger's Archiv*, vol. xxiii.

[3] Oser and Schlesinger, "Experimentelle Untersuchungen über Uterusbewegungen," *Stricker's Med. Jahrbücher*, 1872.

[4] Goltz and Ewald, "Der Hund mit verkürztem Rückenmark," *Pflüger's Archiv*, vol. lxiii., 1896.

[5] Kruiger and Offergeld, "Der Vorgang von Zeugung, Schwangerschaft, Geburt, und Wochenbett an der ausgeschalteten Gebärmutter," *Arch. f. Gynäk.*, vol. lxxxiii., 1908.

[6] Goltz, "Ueber den Einfluss des Nervensystems auf die Vorgänge während der Schwangerschaft und des Gebärakts," *Pflüger's Archiv*, vol. ix., 1874.

[7] Routh, "Parturition during Paraplegia," *Trans. Obstet. Soc. Lond.*, vol. xxxix., 1898.

[8] Brachet, *Recherches*, 2nd Edition, Paris, 1837.

The following general conclusions regarding the nervous mechanism of parturition are based largely on those of Routh. (1) The act of parturition is partly automatic and partly reflex, these actions corresponding in the main to the first and second stages of labour respectively, the spinal reflexes usually commencing as soon as the membranes have ruptured. (2) Direct communication with the brain is not essential for the proper co-ordination of uterine action, but the brain appears to exercise a controlling influence of some kind. Thus, emotions often become a hindrance to the progress of parturition. It would seem possible that this inhibition of uterine contractions is brought about by an inhibition of a centre in the brain (see above, p. 564). (3) Direct communication between the uterus and the lumbar region of the cord is generally essential for the occurrence of those rhythmical contractions which take place during the progress of normal labour. There is experimental evidence upon animals, however, that the uterus is sometimes able automatically to expel its contents, at least as far as the relaxed portion of the genital cord, even when entirely deprived of all spinal influence.[2]

Changes in the Maternal Organism

The influence of parturition upon the metabolism of the maternal organism is dealt with by Sellheim.[3] There is a slight rise of temperature during the process, and the pulse rate is also affected, being much quicker during the pains, but slower between them, the difference amounting to as much as thirty-six beats a minute. The blood shows a marked leucocytosis, and the blood pressure is higher. Urine is secreted in smaller quantities, and is liable to contain traces of renal epithelium, red and white blood corpuscles, and albumen.

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[1] Routh also discusses post-mortem parturition, but points out that in most of those cases where it occurred, the expulsion of the fœtus was caused by increased abdominal pressure due to putrefactive gaseous distension during a condition of muscular relaxation. There are some facts which go to prove that uterine contractility and retraction may continue or even commence after death, possibly resulting from the movements of the imprisoned child.

[2] For further references to the literature of the nervous mechanism of parturition, see Bechterew, *Die Funktionen der Nervencentra*, Weinberg's German translation, vol. i., Jena, 1908.

[3] Sellheim, *loc. cit.*

THE CAUSE OF BIRTH

Foster in his "Text-Book of Physiology"[1] has written as follows: "We may be said to be in the dark as to why the uterus, after remaining for months subject only to futile contractions, is suddenly thrown into powerful and efficient action, and within it may be a few hours, or even less, gets rid of the burden which it has borne with such tolerance for so long a time. None of the various hypotheses which have been put forward can be considered as satisfactory. We can only say that labour is the culminating point of a series of events, and must come sooner or later, though its immediate advent may sometimes be decided by accident." What Foster wrote about this problem is now only partly true, but although progress has been made towards its solution no complete answer has yet been given to the question as to the immediate cause of parturition.

Williams[2] has classified the various theories which have been formulated under eleven heads. These may now be briefly considered in the order adopted by him.

(1) The increasing irritability of the uterus, as manifested by its greater tendency to respond to stimulation in the later stages of gestation, is probably a factor in determining the time of birth. As already described, the uterine contractions towards the close of pregnancy are not only more frequent, but they are also much more intense. This growing irritability is no doubt to be associated in part with the increase in the size of the fœtus.

(2) It is suggested that the mere distension of the uterus must, after a certain point, lead to a reaction, when the organ attempts to reduce itself to its former size, and so expels its contents. This idea receives some support from the fact that twin pregnancies and hydramnios (or the presence of an excessive quantity of liquor amnii) often result in premature labour.

(3) It has been supposed from early times onwards that parturition might be brought about through the pressure of the fœtus producing a gradual dilatation of the cervix. Williams, however, has pointed out that this condition of the cervix cannot be the sole factor, since in a certain number of cases, especially in twin pregnancies, a pronounced dilatation has been known to occur for a considerable period prior to the onset of labour.

(4) Keilmann,[3] working upon the bat, came to the conclusion that the onset of labour was caused by the increasing pressure set up by the lower distended portion of the pregnant uterus (the lower

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[1] Foster, *Text-Book of Physiology*, 5th Edition, vol. iv., London, 1891.

[2] Williams, *loc. cit.*

[3] Keilmann, "Zur Klärung der Cervixfrage," *Zeitsch. f. Geb. u. Gynäk.*, vol. xxii., 1891.

uterine segment) upon the surrounding nerve ganglia. Supposing this conclusion to be correct as applied to the bat, it is not quite clear that it is equally applicable to the human female and to other animals.

(5) Simpson[1] and others were of opinion that the "pains" of labour were the indirect result of a partial separation of fœtus and decidua, brought about by the fatty degeneration of the latter in the last stages of pregnancy, so that the fœtus became virtually converted into a foreign body, which caused the uterus to respond accordingly. It is true that part of the maternal placenta undergoes degenerative changes towards the end of pregnancy, but there is no evidence that this by itself is sufficient to cause a separation of the fœtus from the uterine wall.

(6) There is no evidence in support of the theory that the exciting cause of parturition is an accumulation of carbon dioxide in the blood, beyond the fact demonstrated by Brown-Séquard,[2] Keiffer,[3] and others, that uterine contractions can be induced experimentally by this means.

(7) Spiegelberg[4] put forward the theory that parturition was brought about through the action of substances secreted by the fœtus and passed into the maternal blood. These hypothetical substances, which appear to have been comparable to Starling's hormones, were supposed to act on the uterine centre in the spinal cord. Spiegelberg suggested, further, that the exciting substances were elaborated as a result of an insufficiency of nutrition, and were an indication that the mature fœtus required other sustenance than that supplied to it through the placenta. This theory appears to be devoid of all experimental basis, but it is not opposed by any of the known facts.[5]

(8) Tyler Smith,[6] Minot,[7] Beard,[8] and others have held the view that there is a connection between parturition and menstruation, the two processes being physiologically homologous. According to this theory, there is an increased tendency towards uterine contractions

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[1] Simpson, *loc. cit.*

[2] Brown-Séquard, *Experimental Researches*, English translation, London, 1853.

[3] Keiffer, *loc. cit.*

[4] Spiegelberg, "Die Dauer der Geburt," *Lehrbuch der Geburtshülfe*, vol. ii., 1891.

[5] Van der Heide states that he induced labour pains at full term in pregnant women by injecting fœtal blood-serum. According to the same author the maternal blood of rats in late pregnancy contains substances toxic to non-pregnant animals (*Jour. Med. Research*, vol. xxix., 1914).

[6] Tyler Smith, *Parturition and the Principles and Practice of Obstetrics*, London, 1849.

[7] Minot, "Uterus and Embryo," *Jour. of Morph.*, vol. ii., 1889. "Human Embryology."

[8] Beard, *The Span of Gestation and the Cause of Birth*, Jena, 1897.

at the periods at which menstruation would occur if the condition were not one of pregnancy. Thus Tyler Smith says that there is in all women a greater tendency to abort at the times represented by the catamenial periods. According to Minot, the menstrual and gravitidal changes follow the same cycle of events, the pregnant uterus passing through a prolonged and intensified "menstrual cycle." Consequently, it is probable that there is a common cause for the ending of the series (the casting off of the superficial part of the mucosa *in both cases*). This theory has been further elaborated by Beard, who has arrived at the conclusion that parturition takes place at the time it does in order that a new ovulation may be carried into effect. This author lays great stress upon the rhythmical character of the sexual processes, and points out in support of his theory that "heat" and ovulation frequently ensue shortly after parturition. That this does not happen in many animals has been already shown in the second chapter of this work.[1] Moreover, Beard's theory makes no attempt to explain why parturition should occur in some animals at the close of one particular ovulation interval (*e.g.* in the human species at the close of the tenth), and in other animals at the termination of a different one (that is to say, no explanation is given of the variation in the number of ovulation intervals which are comprised in the period of gestation in different animals). It cannot be said, therefore, that Beard's hypothesis as to the time occupied by gestation and the cause of birth is an adequate one.

(9) Various writers, such as Geyl,[2] have laid some stress upon the belief that parturition occurs in women at a time which has proved, after long ages, to be the most suitable for the perpetuation of the race. A similar statement might of course be made about any other existing species of mammal, for it is only another way of stating the generally accepted belief that parturition, like all other natural phenonema in the animal world, is under the control of natural selection. In support of this contention, as applied to the human species, it has been pointed out that when labour takes place after an abnormally prolonged gestation, it frequently results in dead children, while, on the other hand, premature labour results in puny, ill-developed children, who often perish in early life.

(10) Eden,[3] and also Williams, have pointed out "that the frequent occurrence of infarct formation [*i.e.* a certain kind of

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[1] Beard holds that ovulation takes place shortly after parturition in all Mammals. This is not the case in any monœstrous animals which have a prolonged anœstrous period.

[2] Geyl, "Ueber die Ursache des Geburtseintrittes," *Arch. f. Gynäk.*, vol. xvii., 1881.

[3] Eden, "A Study of the Human Placenta," *Jour. of Path. and Bacteriol.*, vol. iv., 1897.

degenerative change] in the placenta at term must be regarded as evidence of its senility, and that this change is analogous to the obliteration and atrophy of the chorion læve at an earlier period. Where these changes are marked the nutrition of the fœtus must be interfered with, and it is possible that certain of its metabolic products may result in stimulation of the uterine centre."[1] This theory should be compared with that advanced by Spiegelberg (see above).

(11) Lastly, Williams calls attention to the fact that excessive physical fatigue, sudden jars or violence, mental emotion, fright, etc., may lead to the termination of gestation in women. Similarly, it is well known that circumstances of a like nature may induce abortion in animals.

Williams remarks that in all probability the onset of labour in most cases is due to a combination of a number of the abovementioned causes. The main objection to all the theories which have so far been advanced is that they take no account of the complexity of the problem. An hypothesis may be fairly adequate as a general explanation of the duration of gestation, while at the same time taking no account of the immediate cause of birth. Thus, it is no doubt true that the time of parturition is determined largely by the necessities of the offspring, but this conclusion provides no sort of explanation as to why it is that the process in any one particular species generally commences at a certain fixed stage of development, and it remains for us to assume that it is one of the inherent properties of the uterus and correlated organs in the species in question that it should do so. Even on this assumption it is impossible to avoid concluding that there must be some definite exciting cause.

Some light is thrown on this question by the study of the condition of pseudo-pregnancy (see pp. 33 and 36). The three animals in which it is known are the dog, the marsupial cat, and the rabbit (the latter only under experimental conditions). In each of these species during pseudo-pregnancy there is a persistent corpus luteum which at or near the end of the period enters into a state of involution and so probably is in a condition which is not dissimilar to that of the corpus luteum verum at the end of gestation. Furthermore all these animals at the termination of pseudo-pregnancy[2] display habits or instincts which are usually associated with the act of giving birth. Thus the bitch may prepare a bed as if for a litter of pups, the female *Dasyurus* cleans out her pouch as if for the reception of young, and the doe rabbit plucks her breast of fur and uses it to line a nest. Since these habits are displayed at the end of pseudo-pregnancy, which, as we have seen, is dependent on the persistence of the corpus luteum, it is reasonable to suppose that the processes associated with actual parturition after true pregnancy are correlated similarly with changes in the ovarian internal secretions. Ancel and Bouin[1] have supposed that in the first part of pregnancy the tolerance of the uterus for the fœtus is due to the corpus luteum, and in the second half that it is caused by the myometrial gland (see p. 618), but Hammond[2] has shown that it is much more likely that the corpus luteum is the responsible organ throughout the whole of gestation. Further, Sharpey Schafer[3] has shown that the ovaries produce two hormones (see p. 621), one inhibiting the contractility of plain muscle and the other increasing it. Similarly, Guggisberg,[4] by injecting extract of corpus luteum into the extirpated uterus, in some cases obtained increased contraction, in others relaxation. It seems probable that whereas during pregnancy the inhibitory secretion is produced in greatest abundance, at the end of pregnancy the secretion which has an excitatory effect on uterine or other muscle may be dominant in its influence, and so promote the act of giving birth and the processes which are associated with it.

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[1] Williams, *loc. cit.*

[2] In the rabbit about the eighteenth day.

The causes of abortion or premature parturition are discussed below in the chapter on fertility.

PROLONGED GESTATION

The duration of gestation in any one species usually varies within quite narrow limits, but under exceptional circumstances it may continue for an abnormally long period. Thus, Williams[1] records a case of a woman with whom pregnancy extended for over eleven lunar months after the cessation of menstruation, instead of the usual ten lunar months (*i.e.* about 280 days). In this case typical labour pains were experienced at the end of the tenth month, but these subsided after a short time, and were not renewed until four weeks later, when they resulted in parturition. The same woman became pregnant a second time, when the period of pregnancy was again prolonged until the end of the eleventh month after the last menstruation. The children on each occasion were abnormally large and heavy at birth. Allen[2] has recently recorded a number of further cases of prolonged gestation in women, the longest time chronicled being 334 days. It is stated that inertia of the uterus (due to fatty degeneration) is frequently associated with prolonged gestation; but the occurrence of the latter is no doubt often brought about by other causes which are at present unknown.

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[1] Ancel and Bouin, "Sur le Déterminisme de l'Accouchement," *C. R. de l'Acad. des Sciences*, vol. cliv., 1912.

[2] Hammond, "On the Causes Responsible for the Developmental Progress of the Mammary Glands, etc.," *Proc. Roy. Soc.*, B., vol. lxxxix., 1917.

[3] Sharpey Schafer, *The Endocrine Organs*, London, 1917. Itagaki states that extract of corpus luteum generally produces an increase of tone in the uterus, but sometimes the opposite effect is brought about. This difference is not due to condition of pregnancy or non-pregnancy, nor to the strength of the extract, but to differences in the samples of corpus luteum. Extract may produce relaxation in other muscular tissues. Liquor folliculi caused increase in tone of uterine and other muscles. Extract of hilum ovarii (containing interstitial cells) caused inhibition of uterine muscle, but increase of tone in intestine. ("The Influence of Corpus Luteum Extracts upon Plain Muscle," and "On the Action of Various Extracts, etc.," *Quar. Jour. Exp. Physiol.*, vol. xi., 1917.) See also Athias, who describes the effects of various extracts of internally secretory organs upon uterine movements, especially after ovariotomy. ("Effets de la Castration sur les Mouvements Automatiques de l'Uterus chez le Cobaye," *Jour. de Phys. et de Path. Gén.*, vol. xviii., 1919; *Arch. Internat. de Pharm. et de Thér.*, vol. xxv., 1920.) The rhythmical contractions after ovariotomy become enfeebled and eventually die away, but the "tonic" oscillations persist.

[4] Guggisberg, "Ueber die Wirkung der inneren Sekrete auf die Tätigkeit des Uterus," *Zeitsch. f. Geb. und Gyn.*, vol. lxxv., 1913. Extracts of pregnant uterus or of placenta caused contraction.

Cases of prolonged gestation have been observed also among animals. Professor Ewart has informed the writer of a mare in his possession in which the period of gestation was extended to twelve months instead of the usual eleven. Other cases of prolonged gestation in mares, and also in cows, have been recorded by Tessier[3] and Franck-Albrecht-Göring,[4] and appear to be not uncommon. No satisfactory reason has been suggested to account for such cases.

According to Pinard[5] prolonged gestation may occur in Rodents (*Dipodillus simoni*, *Meriones shawi*, *M. longifrons*, *Mus musculus*, etc.), as a result of suckling a large litter produced just previously to a second gestation, as if the development of the young during the latter were arrested by a relative insufficiency of nourishment. In some cases the period of gestation was half as long again as the normal duration.

Kirkham[6] says that with white mice where more than two young are being suckled and the mother becomes pregnant the implantation of the embryos is retarded for about nine days, and until suckling ceases, and that a corresponding prolongation of the period of gestation occurs, as compared with that of non-suckling females. In other cases of suckling mice, according to Kirkham, ovulation is inhibited or postponed. These phenomena are interpreted as being of a protective nature to the parent organism, since mice whose litters are removed at birth usually produce young so frequently that they die of exhaustion before reaching their climacteric.

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[1] Williams, *loc. cit.*

[2] Allen (L. M.), "Prolonged Gestation," *Amer. Jour. of Obstet.*, vol. lv., 1907.

[3] Tessier, "Recherches sur la Durée de la Gestation, etc.," *Mém. de l'Acad. des Sciences*, Paris, 1817.

[4] Franck-Albrecht-Göring, "Die Trächtigkeitsdauer," *Thierärztliche Geburtshülfe*, vol. iv., 1901.

[5] Pinard, Article "Gestation," Richet's *Dictionnaire de Physiologie*, vol. vii., Paris, 1905.

[6] Kirkham, "The Prolonged Gestation Period in Suckling Mice," *Anat. Rec.*, vol. xi., 1916; "The Life of the White Mouse," *Proc. Soc. Exp. Biol. and Med.*, vol. xvii, 1920. Kirkham and also Adler, writing earlier, state that the mammary glands exert an inhibitory influence upon the stimuli coming from the blastula or from the corpus luteum. (Adler, "Versuche mit 'Mammimum Poehl' betreffend die Funktion der Brüstdrüse als innerlich sezernierendes Organ," *Münch. Med. Woch.*, vol. lix., 1912.) That the gestation period in suckling mice is lengthened had been previously noted by Daniel ("Gestation in White Mice," *Jour. Exp. Zool.*, vol. ix., 1910), while Miss King records similar phenomena in white rats (*Biol. Bull.*, vol. xxiv., 1913).

The Puerperium

In multiparous women the uterus continues to contract and relax at more or less regular intervals after the expulsion of the placenta which marks the termination of the third stage of labour. The contractions which occur at this period give rise to the sensations commonly known as the "after-pains." These may last several days, but are not generally very severe after the first day. They are particularly liable to occur when the child is put to the breast, a fact which seems to indicate a nervous connection between the uterus and the mammary glands. In primiparous women the tonicity of the puerperal uterus is usually greater than in multiparous ones, so that the uterus is capable of remaining during this period in a state of almost uninterrupted retraction unless blood clots or other foreign bodies are present in the cavity, in which case the organ undergoes movements in attempting to expel them.

This tonic retraction of the uterus is an important factor in closing the blood sinuses, and so preventing bleeding. If, owing to any circumstance, the normal contraction and retraction of the uterus are interfered with, post-partum hæmorrhage is liable to occur. This is not infrequently the case with white women who have migrated to the tropics, or with ill-nourished women in the slums, in whom, owing apparently to an inefficiency in the uterine nerve supply, the organ tends to become inert.[1] It follows from what has been said that multiparous women are more liable to post-partum hæmorrhage than primiparous ones.[2]

According to Longridge the anæmic condition of the normal puerperal uterus is due partly to the effacement of the ovarian and uterine arteries which occurs when the uterus contracts. "The reality of this occurrence is supported by an observation which can be made in many cases of Cæsarian section; in this operation it is noticed that as long as the uterus remains outside the abdomen it tends to bleed, but that as soon as it is dropped back bleeding ceases. It is not the warmth of the abdominal cavity that checks the bleeding, since it may continue when the uterus is wrapped in warm towels outside the abdomen. But the mere fact of pulling up the uterus opens out the concertina, as it were, and allows blood to flow through the arteries. If the bladder is full at the end of labour, the uterus is pushed upwards, and slight loss may continue until the water is drawn off. As soon as the uterus is allowed to nestle down into its normal position the bleeding stops."[1]

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[1] Longridge, *The Puerperium*, London, 1906.

[2] Longridge has pointed out, however, that the amount of post-partum discharge in multiparæ is not as a rule in proportion to the severity of the "after-pains," and consequently that the latter cannot be ascribed simply to defective retraction on the part of the uterus. He suggests, therefore, that the "after-pains" in multiparæ are largely due to the uterus suffering from cramp resulting from the excessive exertion involved in discharging the child.

The puerperal vaginal discharge is known technically as the lochia. It varies considerably in amount in different individuals, and changes in character as the puerperium proceeds, ceasing altogether about the middle of the third week. For the first few days it consists almost entirely of blood, which makes its way from the raw surface of the uterus and from lacerations caused during delivery. This is the lochia rubra. After three or four days it becomes paler, owing to the dilution of the sanguineous discharge by mucous secretion. This is called the lochia serosa. During the next three days the normal colour of the lochia is brown. This change (from pale pink to brown) is due to the fact that the normal acidity of the vaginal secretion has by this time become re-established. Longridge suggests that the brown colour is probably the result of the formation of some such compound as acid hæmatin. After about the tenth day the lochia assumes a whitish or yellowish-white colour, owing to the admixture of leucocytes and the cessation of the blood flow. It is then known as the lochia alba. In many cases, however, traces of blood may be observed for weeks, but the lochia alba consists mainly of secretions from the vagina and cervix, together with leucocytes, a few epithelial cells, fragments of decidual tissue, and crystals of cholesterin. Micro-organisms are also present in the discharge, but recent investigations have shown that the lochia obtained directly from the uterine cavity does not contain bacteria, excepting in cases where the uterus is the seat of infectious processes.[2]

The average quantity of the discharge has been computed by Gassner[3] at 1485 cubic centimetres, or about 50 ounces. Giles[4] estimated it as 10½ ounces (or considerably less than Gassner's estimation), and found further that in women who were accustomed to bleed freely at the menstrual periods the amount of the lochial discharge was beyond the average. According to Gassner, the discharge is generally less in women who suckle.

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[1] Brock (*Practitioner*, January 1908) has recently expressed the opinion that puerperal bleeding is chiefly venous, pointing out that the discharge is usually very dark in colour.

[2] Krönig, *Bakteriologie des Genitalkanales, etc.*, Leipzig, 1907.

[3] Gassner, "Ueber die Veränderungen des Körpergewichtes bei Schwangeren, Gebärenden, und Wöchnerinnen," *Monatsschr. f. Geburtskunde*, vol. xv., 1862.

[4] Giles, "On the Lochia," *Trans. Obstet. Soc.*, vol. xxxv., 1897.

The uterus after delivery becomes rapidly reduced in size. This process is known as the involution of the uterus; it is completely effected in from five to eight weeks, the greatest reduction taking place in the first few days. Thus the freshly delivered uterus weighs on an average 1000 grammes (or about two pounds), a week later it weighs only half that amount, at the close of the second week 375 grammes, and at the end of the puerperal period as little as 60 grammes (or about two ounces). Its decrease in size is such that by the tenth day after parturition the organ is once more confined to the cavity of the pelvis proper, and cannot be felt above the symphysis.

The process of uterine involution is the result chiefly of changes occurring in the muscle walls.[1] The size of the individual cells becomes very markedly diminished, but there is little or no reduction in their number. Fatty degeneration does not take place in the muscular tissue. It is stated that the retraction of the muscle fibres produces a compression of the vessels, and that the comparatively anæmic condition of the puerperal uterus, especially in the earlier stages, is due to this cause. Subsequently the uterus becomes more vascular again.

The remains of the decidua which are not expelled at parturition undergo degeneration and are discharged in the lochia, leaving only the fundi of the glands and a certain amount of connective tissue from which the uterine stroma is renewed. The epithelium is re-formed from that of the glands, as shown by Friedländer,[2] Kundrat and Engelmann,[3] Leopold,[4] Krönig,[5] and others.[6] Excepting in the position of the placenta, the new epithelium is completely regenerated by the end of the sixth week after delivery.

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[1] The account given of the changes in the uterus during the puerperium is based largely on that given by Williams (*Obstetrics*, New York, 1904). See also Sellheim, "Das Wochenbett," in Nagel's *Handbuch der Physiologie des Menschen*, vol. ii., Braunschweig, 1906, where further references are given.

[2] Friedländer, *Physiologische und Anatomische Untersuchungen über den Uterus*, Leipzig, 1870.

[3] Kundrat and Engelmann, "Untersuchungen über die Uterusschleimhaut," *Stricker's Med. Jahrbuch*, 1873.

[4] Leopold, *Studien über die Uterusschleimhaut, etc.*, Berlin, 1878.

[5] Krönig, "Beitrag zum anatomischen Verhalten der Schleimhaut der Cervix und des Uterus, etc.," *Arch. f. Gynäk.*, vol. lxiii., 1901.

[6] Leusden, assuming the syncytial tissue of the deciduum to be of maternal origin, has suggested that it may assist in giving rise to the new epithelium ("Ueber die Serotinalen Riesenzellen, etc.," *Zeitsch. f. Geb. und Gynäk.*, vol. xxxvi., 1897).

The placental area at the end of parturition is marked by the presence of thrombosed vessels. It is raised above the general surface of the uterine wall, and is irregular in shape. It very soon diminishes in size, its diameter being not more than two centimetres long at the end of the puerperal period, although its former position may be detected as an area slightly stained by blood pigment for several months after delivery.

Williams states that in the last month of pregnancy some of the sinuses at the placental area undergo thrombosis, but that this process becomes much more marked after the completion of labour, although many of the sinuses are simply compressed by the contracting uterine muscles without ever becoming thrombosed.[1] The thrombi are eventually converted into ordinary connective tissue by a cellular proliferation from the lining membrane of the vessel.s While this change is in progress the lining membrane presents a folded appearance somewhat resembling a typical developing corpus luteum. This is especially well seen about the fourth week after parturition, but even up to the end of a year the convoluted appearance is still sometimes discernible.[2] The lumina of the arteries become reduced in size, but the thickening of their walls, which takes place during pregnancy, is an alteration of a more permanent character. This histological change affords a means of discriminating between a virgin and a parous uterus.

Leo Loeb and Huramitau[3] have studied the involution of the uterus in the guinea-pig and find that it is favoured by suckling. They regard the effect on the uterine tissues as acting directly, and not indirectly by way of the ovaries. Castration is stated to favour uterine involution in the guinea-pig.

The human cervix remains for some time after delivery as a soft flaccid structure with lacerated edges, but it gradually undergoes involution, the lumen becoming narrower. The vagina takes about the same time to recover as the uterus. After a first delivery its outlet remains permanently wider than before. The rugæ reappear about the third week. The place of the hymen is taken by numerous small tags of tissue which become transformed into the carunculæ myrtiformes. The condition of the labia majora and labia minora is generally flabby and atrophic as contrasted with that existing in virgin women.

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[1] According to Longridge (see below in the text), thrombosis is of little or no importance in assisting the hæmostasis of normal labour.

[2] Williams (Sir J.), "Changes in the Uterus, etc.," *Trans. Obstet. Soc.*, vol. xx., 1878. See also Helme, "Histological Observations, etc.," *Trans. Roy. Soc. Edin.*, vol. xxxv., 1890.

[3] Huramitau and Leo Loeb, "The Involution of the Uterus following Labour," *Amer. Jour. Physiol.*, vol. lv., 1921.

The characteristic changes which occur in the breasts in connection with the secretion of milk are described in the next chapter.

The quantity of urine passed during the first two days of the puerperium is generally above the average. The urine frequently contains sugar, which may be either glucose or lactose. In the latter case it is generally believed that the sugar has been absorbed into the circulation from the changed mammary glands. When glycosuria occurs, it is probably comparable to post-operative glycosuria (see p. 539 and pp. 602-604). Albumen may also be present in the urine in the first days of the puerperium. It is stated further that there is an increase in the amount of acetone[1] (see also p. 535).

As mentioned above, a marked leucocytosis occurs during labour. According to Hofbauer,[2] this becomes still more pronounced during the first twelve hours of the puerperium, after which the number of leucocytes in the blood falls again and in a short time becomes normal. Henderson[3] states that on the fifth day the average number of leucocytes per cubic millimetre is 12,000, whereas immediately after parturition it is 21,000, as compared with about 8000 in a normal woman. It is stated that there is a diminution in the number of red corpuscles during the first days of the puerperium, a circumstance which is commonly ascribed to the loss of blood at delivery and the lochial discharge. It is also said that the amount of hæmoglobin is reduced, and that there is a relative increase in the quantity of fibrin and serum. Experiments show, however, that there is no appreciable shortening in the coagulation-time of the blood, such as has been supposed to account for the thrombosis of the sinuses.[4]

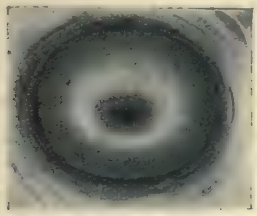

FIG. 160.—Virginal external os (human). (From Williams' *Obstetrics*. Appleton & Co.)

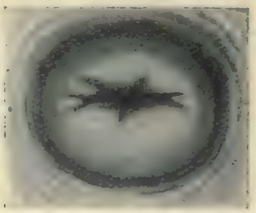

FIG. 161.—Parous external os (human). (From Williams' *Obstetrics*. Appleton & Co.)

The pulse rate during the early days of the puerperium is usually stated to be somewhat below the normal, but according to Longridge such cases are unusual. Williams[1] says that the pulse is slowest on the second or third day, after which it becomes quicker, resuming its normal rate after about ten days.

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[1] Scholten, "Ueber Puerperale Acetonurie," Hegar's *Beiträge zur Geb. und Gynäk.*, vol. iii., 1900.

[2] Hofbauer, "Zur Physiologie des Puerperiums," *Monatsschr. f. Geburt. und Gynäk.*, vol. v., 1897.

[3] Henderson, "Observations on the Maternal Blood at Term and during the Puerperium," *Jour. of Obstet. and Gynæc.*, vol. i., 1902.

[4] Longridge, *loc. cit.*

The temperature is ordinarily normal during the puerperium, the old idea that the commencement of milk secretion was associated with a rise of temperature having apparently no basis in fact, excepting in cases of infection.

Little attention has been paid to the changes which occur during the puerperal period in other animals. Strahl has shown[2] that the Mammalia with so-called full placenta (commonly called Deciduata) can be arranged under three groups according to the process of puerperal involution of the uterus. In the first group, to which man and monkeys belong, the epithelium is absent from the mucosa, and requires, therefore, to be re-formed in the manner described above. In the second group the placenta is spread out over the inside of the uterus as in the first group, but in addition to this the inside of the organ is covered by a layer of epithelium. This arrangement is found in Carnivores. In the Rodents we often meet with the third form; here, towards the end of gestation, not only is the womb covered with cell-tissue, but this epithelium also runs from the fimbriæ right underneath the placenta, undermining it till it is finally only adhering to the walls of the uterus by a slender cord carrying the vessels. It is evident, therefore, that the uteri of the second and third groups will resume relatively quickly their non-puerperal appearance. The principal changes that occur are the reduction of the surface epithelium both by the casting off of superfluous parts and by the changing of larger cells into smaller ones, the advance of new epithelium to cover places that were bare,[3] and the reduction and consolidation of the connective tissue. The latter process is effected by the cells becoming more compact, as in the bitch, or by a reduction in the amount of intercellular substance, as in the hedgehog.[4] The puerperal changes in *Tarsius* are said to resemble those of Rodents.[5] Excepting in those animals which belong to the first group mentioned the lochial discharge is either very slight or absent altogether.

The changes which take place in the uterus after abortion have been studied by Weymeersch,[1] who states that the placenta may for a time persist. If the abortion is produced experimentally by the removal of the ovaries the absence of the corpus luteum results in an immediate contraction of the uterine vessels as well as of the uterine muscle wall. Fortayn[2] also states that the chorion survives after the death of the embryo in the mouse.

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[1] Williams (Whitridge), *loc. cit.*

[2] Strahl, "The Process of Involution of the Mucous Membrane of the Uterus of *Tarsius spectrum* after Parturition," *Proc. Section of Sciences, Koninklijke Akademie van Wetenschappen te Amsterdam*, vol. vi., 1904.

[3] Duval, "De la Régénération de l'Épithélium des Corne utérine après la Parturition," *C. R. de la Soc. de Biol.*, vol. ii., Series 9, 1890.

[4] Strahl, "The Uterus of *Erinaceus europæus* after Parturition," *Proc. Sect. Sciences, Kon. Akad. Wet. Amsterdam*, vol. viii., 1906.

[5] For the puerperal changes in *Tupaia* see van Herwerden, *loc. cit.*

The changes which take place in connection with the formation of milk in animals are described in the next chapter.

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[1] Weymeersch, "Etude sur le Méchanisme de l'Avortement, etc." *Thèse* Université de Bruxelles, Paris, 1911. See also *Jour. de l'Anat. et Phys.*, vol. xlvii., 1911.

[2] Fortayn, "The Involution of the Placenta in the Mouse after the Death of the Embryo," *Archiv. de Biol.*, vol. xxx., 1920.

CHAPTER XIII

LACTATION

> "Nunc femina quæque,
> Cum peperit, dulci repletur lacte, quod omnis
> Impetus in mammas convertitur ille alimenti."
>
> —LUCRETIUS.

THE possession of mammary glands is an essentially mammalian character. Their function is to provide nourishment for the newly-born young. They are present in both sexes, but are usually functional in the female only. Their number and position vary considerably in different species. There may be only a single pair (man), or as many as eleven pairs (*Centetes*). The number in any particular species usually bears a relation to the normal size of the litter, or to the requirements of the newly-born offspring. Thus in the guinea-pig, in which the young are born in an advanced state of development, and can feed without being suckled, there are only two mammary glands, while in the rabbit, in which the newly-born young are naked and helpless and the gestation period is far shorter, there are seven or eight mammæ. In animals which possess a number of mammary glands, these are usually arranged in two nearly parallel rows along the ventral side of the thorax and abdomen. In other cases they are restricted to the thorax (Primates, excepting some lemurs, Cheiroptera, Sirenia, elephants, sloths); while in others again they are confined to the inguinal region (most Ungulates, Cetaceans).

In the cow and most other Ungulates the mammæ are contained within a definite milk-bag or udder, which is surrounded by a fibrous envelope and is suspended below the abdomen. The udder is provided with milk cisterns or galactophorous sinuses into which the ducts of the gland open and convey the milk from the secretory acini. Each sinus communicates with the exterior by a teat, there being four teats in a cow, corresponding to the four mammary glands (and sinuses) commonly called the four "quarters." One quarter may run dry without the others. There is a fibrous division consisting of yellow elastic tissue between the two lateral halves of the cow's udder, but not between the anterior and posterior parts. There are very frequently extra teats (sometimes as many as three) situated posteriorly (or one may be between two of the chief teats) and with glands associated with them. During lactation these extra glands may secrete, but the milk or other fluid secreted by them, since it is not usually drawn off, is absorbed into the circulation (see below, p. 603). In the sheep there are only two glands (lateral halves), sinuses, and teats (occasionally four), and the mare is similar excepting that there may be two or even four sinuses opening into one teat. In the sow the teats extend forward to the thorax in two rows. In many animals there is a sphincter at the end of each teat.

In Monotremes the mammary glands are stated to be modified sweat glands, whereas in other mammalian orders they are commonly regarded as representing sebaceous glands.[1] In Monotremes alone there are no teats, the orifices of the glands being mere scattered pores in the skin, the exuding milk probably passing along the hairs, which in this region are arranged in bunches. In *Echidna* the orifices open into two depressions which have been called the mammary pockets.[2] Teats, which are present in all other orders of Mammals, are of two kinds. In one kind the skin in the region of the gland becomes raised up in a circular rim, and in this way gives rise to a tubular teat or nipple, into the base of which the ducts of the gland open. This form of teat occurs in Carnivora and Ungulata. In the other kind of teat the gland itself is raised into a papilla, as in man and other Primates, in Rodents and in Marsupials. The use of the teats is to facilitate the process of sucking. In the Cetacea, however, where the action of sucking is incompatible with the subaqueous life of these animals, the ducts of the mammary glands are enlarged into reservoirs (somewhat similar to the galactophorous sinuses of Ungulates), from which the milk is ejected into the mouths of the young by means of a compressor muscle.[3]

In the male mammal, as just mentioned, the mammæ do not usually function, though milk is occasionally produced in man at birth and at puberty, and more rarely at other times. Male goats and sheep have been known to yield milk exceptionally, and the same is also said to be the case with male rats[4] (see p. 614).

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[1] Brouha and certain other authorities regard the mammary glands in all the Mammalia as modified sweat glands ("Recherches sur les Diverses Phases du Développement et de l'Activité de la Mamelle," *Arch. de Biol.*, vol. xxi., 1905. This paper contains many references). Eggelung regards the mammary glands either as homologous with sweat glands, or else as organs which are *sui generis*, being derived independently from the primitive merocrine skin-gland ("Ueber den wichtigen Stadium in der Entwickelung der menschlichen Milchdrüse," *Anat. Anz.*, vol. xxiv., 1904).

[2] Wiedersheim, *Comparative Anatomy of Vertebrates*, Parker's translation, 2nd Edition, London, 1897.

[3] Flower and Lydekker, *An Introduction to the Study of Mammals*, London, 1891.

[4] Wiedersheim, *loc. cit.*

STRUCTURE OF THE MAMMARY GLANDS

The mammary glands are composed typically of a number of lobes, which are themselves divisible into lobules. Each lobule consists of connective tissue in which the convoluted ducts of the gland are bound together. If these ducts are traced backwards they are seen to arise from groups of secretory alveoli. If they are traced forwards they are found to unite together to form the lactiferous ducts, which in the human subject are from fifteen to twenty in number, and open to the exterior by minute apertures through the teat. The lactiferous ducts at their point of origin from the lobular ducts are provided with reservoirs in which the milk collects during the periods of glandular activity (*i.e.* during lactation). These reservoirs in some animals are of a very considerable size (*e.g.* whales, as described above). The duct walls consist of areolar tissue containing some unstriated muscle fibres. They are lined internally by short columnar epithelial cells which become flattened in the proximity of the nipple. A quantity of fat generally covers the surface of the gland, excepting the nipple. This fat is connected both with the skin in front and with the glandular tissue behind. Like the latter it is lobulated by processes of areolar tissue. The nipple also is formed of areolar tissue with unstriated muscle fibres. It is richly supplied with vessels which give it an erectile structure. The glandular tissue also is plentifully supplied with vessels, which vary in size according to the condition of the gland. The glands in man are innervated by branches from the anterior and lateral intercostal cutaneous nerves. Sensitive papillæ are present on the surface of the nipple, and around it there is a small area of skin, on which the ducts of little secretory glands open to the exterior.

In the sow the mammary glands are often pigmented, and the bacon cut from this area is discoloured, the condition being known among bacon-curers as "seedy-cut." It was formerly supposed that the pigment was blood pigment derived from red corpuscles extravasated during "heat," when the glands are apt to be congested, and that it did not occur in pigs which had been subjected to ovariotomy. It is now known, however, that the pigment is not derived from blood (thus, it does not contain iron) and that it may occur in spayed sows and even in males, but it is always in association with mammary tissue. It has been identified by Hammond in fœtal pigs in the walls of the developing ducts as they dip down from the skin. The pigment is presumably identical with that of the hair since it only occurs in coloured pigs, and in Red Tamworths is of a sandy colour.[1]

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[1] Mackenzie, Marshall, and Hammond, "On Ovariotomy in Sows, etc.," *Jour. Agric. Science*, vols. iv., 1911-12; v., 1912-13; vi., 1914; and vii., 1915-16; and "Physiology and Bacon Curing," *Jour. Roy. Agric. Soc.*, vol. lxxvi., 1915.

In the secretory cells of the lactating mammary gland an active and a resting condition can be distinguished. In the latter the lumina of the alveoli are wide, and the cells of the lining epithelium form a single flat layer with centrally situated nuclei. In the active condition the epithelial cells are long and columnar, and project into the lumina, and some of them have two nuclei.

In these cells numbers of granules and globules accumulate, the former being probably of a protein nature, and the latter of a fatty composition. Gradually the alveoli become charged with a fluid containing detached cells and fatty globules. The detached cells are usually filled with granules, staining with osmic acid and seemingly identical with the colostrum corpuscles which have been observed to occur in milk in the first few days after parturition, and occasionally also at other times. These colostrum corpuscles have been seen to exhibit amœboid movements, and so are probably leucocytes which have wandered into the lumina of the alveoli.[1] The secretory fluid also contains cells which are supposed to have been detached from the epithelium, but, as will be seen presently, there is some doubt regarding this point.

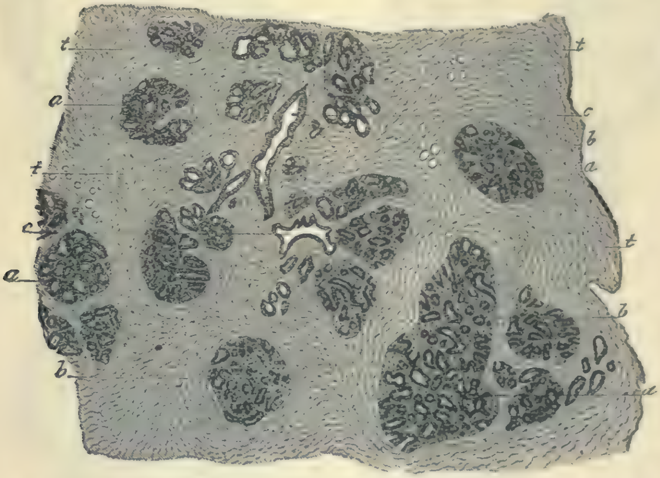

Fig. 162.—Section of mammary gland of woman. (From Sharpey Schafer, after de Sinéty.)

a, Lobule of gland ; *b*, acini lined by cubical epithelium ; *c*, duct ; *t*, connective tissue.

The alveoli secrete milk during lactation, not merely while suckling is going on, but also at other times, so that milk tends to collect in the ducts and especially in the reservoirs. It has been calculated that the udder of a cow could not contain the quantity of milk which can be obtained from it at one milking, so that in such cases at least it seems certain that the process of secretion must be carried on during the time that the milk is being drawn. Furthermore, the milk which is drawn latest has been shown to have a different composition from that which is first obtained, the proportion of solids to liquids undergoing an increase as the process of milking is continued. This, however, is believed to be due partly to the larger globules of fat meeting with greater resistance in passing through the ducts and so being retained until the end of milking. Lehmann[1] has recorded an experiment in which a solution of sulphindigotate of sodium was injected into a vein of a goat which was immediately afterwards milked. By the time the udder had been almost completely emptied, a blue tinge appeared in the milk. After an interval of about an hour and a half the animal was again milked, when it was found that the injected sulphindigotate had penetrated in sufficient quantity to render the milk quite blue.

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[1] Sharpey Schafer, "The Mechanism of the Secretion of Milk," *Text-Book of Physiology*, vol. i., Edinburgh, 1898.

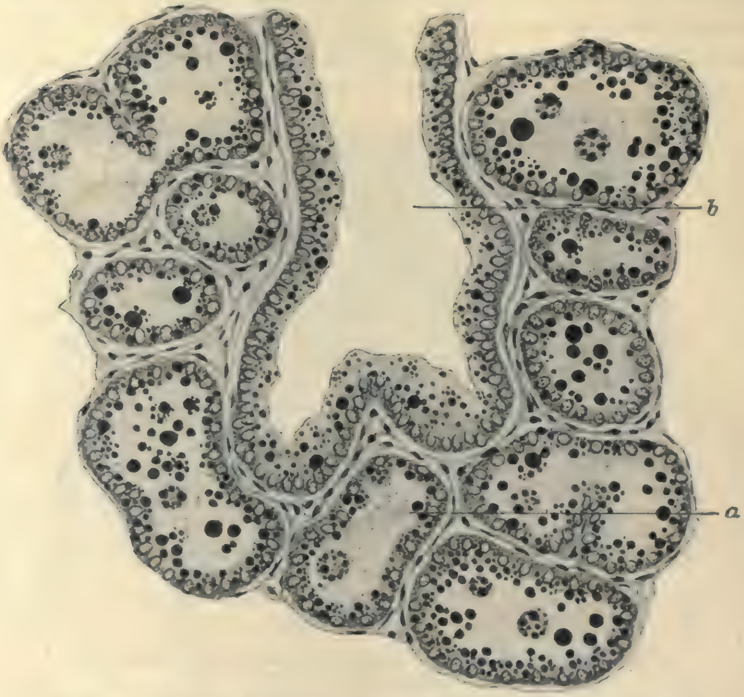

FIG. 163.—Section of mammary gland (human) during lactation (highly magnified). *a*, Acini ; *b*, duct.

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[1] Lehmann, "Beiträge zur Physiologie der Milchbildung," *Die landwirthschaftlichen Versuchs-Stationen*, vol. xxxiii., 1887.

Three different hypotheses have been put forward regarding the manner in which the substances of which the milk is formed pass out from the secretory cells. According to one view, the cells themselves break loose and become disintegrated, setting free their contents in the alveoli of the gland, just as in the case of the sebaceous glands.

Another theory states that the cells simply excrete the substances into the alveolar lumina without becoming detached or destroyed themselves, as with the submaxillary mucous gland. According to the third hypothesis the mammary gland in its mode of activity occupies a position midway between the sebaceous and submaxillary glands; some of the cells simply discharging their contents into the lumina, while with others, the central part of the cell, containing a degenerate daughter nucleus, breaks away and becomes disintegrated, leaving the basal portion still in position.

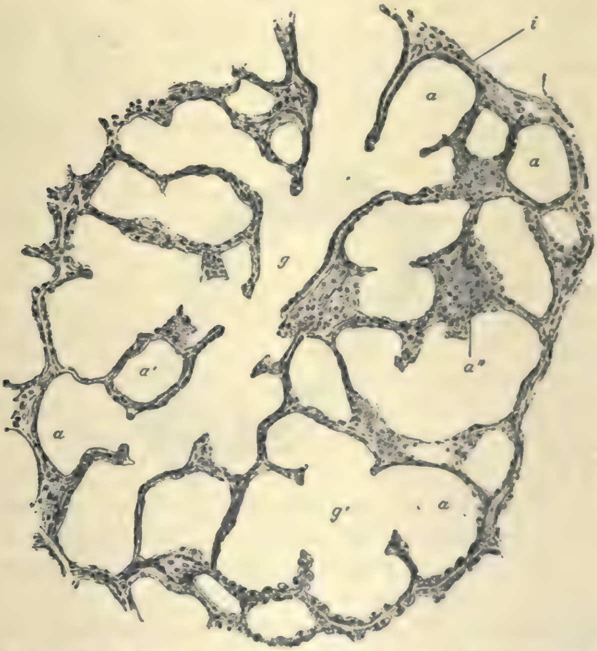

FIG. 164.—Section of mammary gland (human) in full activity. (From Sharpey Schafer, after von Ebner.)

a, *a'*, *a''*, Alveoli variously cut and distended by secretion; *g*, *g'*, commencing ducts; *i*, connective tissue.

It has already been mentioned that the mammary glands of all Mammals, with the exception of the Monotremes, are usually regarded as being of the nature of modified sebaceous glands. It was partly on account of this belief that certain of the older writers held the view that the secretion of milk was the result of a fatty degeneration leading to a complete disintegration of the secretory cells of the mammary gland.[1] According to this theory the colostrum corpuscles were the detached epithelial cells. In opposition to this theory, it has been pointed out that there is no evidence of the extensive cell multiplication, such as would be required in order to supply the large number of cells which, according to this hypothesis, would necessarily become detached. Heidenhain[2] has shown that if this theory is correct, the cells of the gland must be completely renewed as often as five times in one day in order to provide the solid constituents of the secretion.

The second of the above-mentioned theories receives considerable support from the circumstance that it has the analogy of the great majority of secretory glands.[3] Moreover, the results of Bertkau's[4] investigation point strongly to the conclusion that any appearances of disintegration which the secretory cells possess are due to imperfect fixation. This author states that he found no necrobiosis of any kind in these cells, and he believes that milk formation is a purely secretory process. This view is now widely accepted and the colostrum corpuscles are regarded as of the nature of wandering leucocytes.

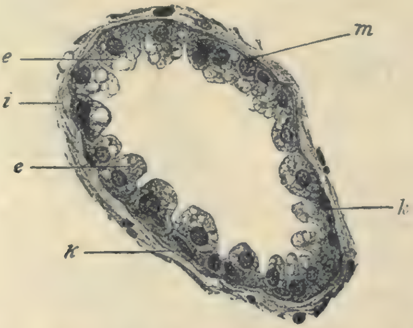

FIG. 165.—Section through an alveolus with fat drops in cells. (From Sharpey Schafer, after von Ebner.)

e, Cells of alveolus ; *k*, cells of basement membrane (*m*) ; *i*, connective tissue.

The third theory was first suggested by Langer, and has since been adopted, with various slight modifications, by Heidenhain,[5] Steinhaus,[6] and Brouha[7] and others. According to their view the cells of the gland lengthen out, so that their ends come to project freely into the lumina of the alveoli. The projecting portions then undergo a process of disintegration before or after becoming detached, and the cell substance passes into solution to form the albuminous and carbohydrate constituents of the milk. The fat droplets which collect in the disintegrating part of the cell give rise to the milk fat. The basal portions of the cell remain in position without being detached, and subsequently develop fresh processes, which in their turn become disintegrated. It is believed, however, that some cells simply discharge their fat droplets and other contents into the lumina, while otherwise remaining intact.[1]

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[1] Virchow, *Die Cellular-Pathologie*, Berlin, 1871.

[2] Heidenhain, "Die Milchabsonderung," *Hermann's Handbuch der Physiologie*, vol. iv., 1883.

[3] Sharpey Schafer, *loc. cit.*

[4] Bertkau, "Ein Beitrag zur Anatomie und Physiologie der Milchdrüse," *Anat. Anz.*, vol. xxx., 1907.

[5] Heidenhain, *loc. cit.*

[6] Steinhaus, "Die Morphologie der Milchabsonderung," *Arch. f. Anat. u. Phys.*, Phys. Abth., Suppl., 1892.

[7] Brouha's paper (*loc. cit.*) contains a full account of the literature.

Steinhaus states that mitotic division of the cell nuclei in the actively secreting mammary glands is of frequent occurrence, and that the daughter nuclei which lie in the outer portions of the cells degenerate and share in the general process of dissociation. Szabó[2] also records the occurrence of two or more nuclei in the same cell during lactation, and similar evidence of nuclear division has been observed by others. Moreover, it is argued that this view is in no way inconsistent with the generally accepted homology between the mammary and sebaceous glands, since it is easy to understand how, in the course of evolutionary development, the mode of secretion in the glands in question might have undergone an alteration, whereby the process of disintegration in the actively secreting cells became gradually lessened as the character of the secretion changed. On the other hand, if we suppose that the cells of the mammary gland merely extrude their secreted materials without undergoing any histological disintegration, it is more difficult to uphold the homology in question. Lastly, it should be mentioned that those who, like Steinhaus, support the theory of partial disintegration, do not regard the colostrum corpuscles as detached epithelial cells, as Heidenhain did, but agree with those who uphold the purely secretory theory in supposing the corpuscles to be of the nature of "mast cells," or basophil leucocytes which have wandered inward from the connective tissue of the gland, as already described, and have made their way into the lumina of the alveoli.[3]

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[1] Brouha, *loc. cit.*; also "Les Phénomenès histologiques de la Sécrétion lactée," *Anat. Anz.*, vol. xxvii.

[2] Szabó, "Die Milchdrüse im Ruhezustande und während ihrer Thätigkeit,' *Arch. f. Anat. u. Phys.*, Anat. Abth., 1896.

[3] For references to further literature upon the physiology of milk formation see Basch, "Die Physiologie der Milchabsonderung," *Ergeb. des Phys.*, 1903, Jahrg. See also the following for references to the histology: Bizzorzero and Ottolanghi, "Histologie der Milchdrüse," Merkel and Bonnet's *Ergeb. d. Anat. u. Entwick.*, vol. ix., 1900, and von Ebner, "Von den Geschlechtsorganen," Kölliker's *Handbuch der Gewebelehre des Menschen*, vol. iii., 1902.

The Composition and Properties of Milk

Milk is essentially an emulsion, its white appearance being caused by the reflection of the innumerable fat globules which it contains in suspension. These globules, which are from ·0015 to ·005 millimetre in diameter, tend to float chiefly at the top, where they help to form the cream, or that part of the fluid which is richest in fatty constituents. The specific gravity of both human and cow's milk is from about 1·028 to 1·034.[1] When the cream is skimmed off the specific gravity of course rises.

It is not proposed in the present work to deal more than very briefly with the composition and properties of milk in different animals.[2] Human milk and cow's milk have been most fully investigated, and it will suffice in this place to give a short account of their respective constituents.

The average composition of cow's milk as compared with human milk is as follows:—

	Cow's.	*Human.*
Water - - - - - -	88·3	88·8
Proteins - - - - -	3·0	1·0
Fats - - - - - -	3·5	3·5
Carbohydrates - - - -	4·5	6·5
Salts - - - - - -	0·7	0·2
	100·0	100·0

The proteins of milk are caseinogen, lactalbumen, and lactoglobulin. Of these caseinogen is the most important. This is the substance which is acted on by the ferment of rennet, producing the well-known clotting or curding of milk, when the caseinogen is converted into whey albumen and insoluble casein. Lactoglobulin and lactalbumen are only present in small quantities.

The fats of milk, which occur in small globules as just described, are olein, palmatin, and stearin, with small quantities of butyrin, capronin, and other fats of lower composition. Lecithin and cholesterin are also present in small amounts, at any rate in cow's milk. The percentage of volatile fatty acids is less in human than in cow's milk.

Lactose or milk-sugar is the carbohydrate of milk, but other carbohydrates (animal gum, dextrin, etc.) have also been stated to occur. Lactose under the influence of certain micro-organisms becomes converted into lactic acid, which causes the souring of milk.

Milk is rich in calcium and potassium salts (especially in calcium phosphate), but magnesium, sodium, and other salts (chiefly chlorides) are also present in small quantities. The amount of iron in human milk is very slight, while in cow's milk it is practically absent altogether.

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[1] Halliburton, "The Chemical Constituents of the Body and Food," Sharpey Schafer's *Text-Book of Physiology*, vol. i., Edinburgh, 1898.

[2] See Halliburton, *loc. cit.*, and Sharpey Schafer.

Bunge[1] has pointed out that whereas the inorganic salts in milk are present in different proportions from those found in the blood plasma, these proportions are almost identical with those occurring in the young animal. He supposes this similarity to indicate an adaptation to the needs of the young. This point is illustrated in the following table, which gives the respective amounts of mineral constituents present in a hundred parts of ash of (1) the young pup, (2) dog's milk, and (3) dog's serum.

	(1) *Young Pup.*	(2) *Dog's Milk.*	(3) *Dog's Serum.*
K_2O	8·5	10·7	2·4
Na_2O	8·2	6·1	52·1
CaO	35·8	34·4	2·1
MgO	1·6	1·5	0·5
Fe_2O_3	0·34	0·14	0·12
P_2O_5	39·8	37·5	5·9
Cl	7·3	12·4	47·6

Small quantities of oxygen, nitrogen, and carbon dioxide gases have been found in solution both in human and in cow's milk.

The chief difference in the composition of cow's milk as compared with human milk is the relatively high percentage of proteins, fats, and salts, and the correspondingly low percentage of lactose present in cow's milk.

Colostrum is the milk which is secreted during the first two or three days after parturition. It contains less caseinogen than ordinary milk, but considerable quantities of albumen and globulin enter into its composition. It coagulates on boiling. The characteristic colostrum corpuscles have already been described.

The mammary glands of newly-born animals sometimes secrete small quantities of what is popularly called "witches' milk." This secretion contains most of the constituents of normal milk, but the solid substances are usually less in amount. It has an alkaline reaction.[2]

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[1] Bunge, *Lehrbuch der Physiologischen und Pathologischen Chemie*, Leipzig, 1887, and various original papers. *Cf.* Abderhalden, "Die Beziehungen der Wachsthumsgeschwindigkeit der Säuglinge zur Zusammensetzung der Milch, etc.," *Zeitsch. f. physiol. Chem.*, vol. xxvi., 1899, and other papers by the same author in the same journal (vols. xxvi. and xxvii.). For further references see Lusk, *The Science of Nutrition*, Philadelphia, 1906. It is stated also that the rennin of the stomach is specifically adapted for the coagulation of the casein produced by the female of the same race.

[2] For fuller information about the constituents and properties of milk, with tables of composition for different animals, and numerous references to the literature, see Halliburton, *loc. cit.* See also Raudnitz, "Bestandteile, Eigenschaften und Veränderungen der Milch," *Ergeb. der Phys.*, 1903, Jahrg. 2, where certain later papers are referred to; and Abderhalden, *loc. cit.*

THE INFLUENCE OF DIET AND OTHER FACTORS ON THE COMPOSITION AND YIELD OF MILK

The composition of the milk in any one species is subject to some amount of variation, which is due to various causes. Thus, the differences in the composition of cow's milk are said to depend on the following factors: (1) The breed, (2) The advance in the period of lactation, (3) The season of the year, (4) The length of the interval between the times of milking, (5) The occurrence of sexual excitement, (6) Situation and climate, (7) Meteorological changes, and (8) The character of the food.[1] These factors may now be briefly discussed.

That the yield and composition of the milk varies in the different breeds is generally admitted. Thus Jersey cows yield a larger proportion of butter fat than Ayrshires. Within the limits of the breed also there is great individual variation and heredity plays an important part.[2] But of all the factors enumerated above, diet is perhaps the most important. The richest and also the most abundant supply of milk is usually yielded when the food supply is liberal. As a result of giving food rich in protein substances, the milk supply tends to contain a larger quantity of protein, sugar, and fat (especially the latter). Sharpey Schafer has pointed out, however, that because an excess of a particular organic principle in the food causes an increase of certain constituents in the milk, it must not be supposed that these constituents are necessarily formed directly from such material, "for the effect may be produced indirectly by the functions of the gland-cells becoming modified, according to the nature of the pabulum they are receiving. Looked at in this light, certain substances may be said to stimulate the cells of the glands to increased activity in all directions, tending to the production of a larger quantity of milk rich in all kinds of solid constituents; whilst other substances may be looked upon as stimulating the cells in a special manner, tending to the increased production of certain only of the constituents of the milk."[1]

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[1] Crowther, *Milk Investigations at Garforth*, Leeds, 1904. Droop Richmond, "The Composition of Milk," *Analyst*, vol. xxxi., 1906. Lauder, "The Variation in the Composition of Milk," Bulletin XI. issued by the Edinburgh and East of Scotland College of Agriculture, 1906. Crowther, "The Chemical Composition of Butter," *Trans. Highland and Agric. Soc.*, vol. xix., 1907. Gilchrist and Jones, "Dairy Investigations in the North-East of England," *Trans. Highland and Agric. Soc.*, vol. xviii., 1906, and vol. xix., 1907.

[2] Gavin has dealt with the question of estimating a cow's milking capacity by her first lactation yield, and has come to the conclusion that with cows giving a fairly high or fairly low first lactation revised maximum, this figure should be used to determine whether they should be kept or not, but with cows giving a medium first lactation revised maximum, it is worth waiting to obtain the increased accuracy of an estimate based on the mean between the first and second lactation revised maxima. (The "Revised Maximum" is defined as the maximum day-yield of the lactation which is three times reached or exceeded, *i.e.* the highest figure common to the three highest day-yields of a lactation.) Gavin thinks that the maximum yield is a better indicator of physiological capability than the average yield, and therefore a better guide as to whether a cow should be kept. ("Studies in Milk Records," *Jour. Agric. Science*, vol. v., 1913.)

According to Crowther's researches on cows, change from a highly nitrogenous diet to one relatively poor in nitrogen causes secretion of a greater quantity of milk, but there is a decrease in the fat content, this being more pronounced in the morning than in the evening milk. A change in the reverse direction effected an improvement in the quality of the milk. Concentrated food given either in the morning or evening tended to increase the fat content of the morning milk, but had little or no effect upon the evening milk. These alterations were found to persist without appreciable diminution for fully five weeks after the change of treatment.

There are a number of preparations in the market, known as galactogogues, which are said to increase the flow of milk in women, but, according to Williams, any virtue which they possess is due largely to the quantity of fluid which is taken with them.[2] It is stated also that certain particular food-stuffs have a very appreciable effect upon the quantity and quality of milk in cows. Thus bean-meal is said to increase the flow of really good milk, unless it is given in immoderate quantities. Brewers' and distillers' grains are likewise described as having a beneficial influence upon the milk supply, but if given too freely they tend to injure the breeding capacity, and in consequence are most used in town dairies where the cows are not bred from.[3] Many substances ingested by the mother pass unaltered into the milk. It is well known that certain foods (*e.g.* turnips) cause an unpleasant taste or smell in the milk of cows to which they are supplied. Lehmann's experiment, in which sodium sulphindigotate was injected into the veins of a goat, and shortly afterwards made its appearance in the milk, has already been referred to (p. 590). So also it has been found that immunity from disease may be acquired by young animals being suckled by a female which had previously become immune, the antibody to the disease being absorbed in the ingested milk.

It is generally recognised that the nature of the surroundings has an influence over the mammary secretion. For example, the composition of the fat in the milk of cows varies with the condition of the animals. Circumstances tending to cause discomfort usually lower the proportion of volatile acids present in the butter fat, but the variation in the composition is very irregular, and appears to depend partly upon the nervous temperament of the cow. Extremes of heat and cold are said to produce a decrease in the percentage of volatile acids, a fact which has been put forward as an explanation of the general poorness in these compounds of butters from Siberia and other cold climates. Unseasonable and inclement weather is believed to have a similar influence.[1]

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[1] Sharpey Schafer, *loc. cit.* There is evidence also that an abnormal diet during and previous to pregnancy may arrest the normal mammary development. See Watson (B. P.), "The Effect of a Meat Diet on Fertility and Lactation," *Proc. Roy. Soc. Edin.*, vol. xxvii., 1907. For general literature see Meigs, "Milk Secretion as Related to Diet," *Physiological Reviews*, vol. ii., 1922.

[2] Williams (W.), *Obstetrics*, London, 1904.

[3] Wallace (R.), *Farm Live Stock of Great Britain*, 4th Edit., Edinburgh, 1907.

In women exercise in the open air may not infrequently increase the flow of milk. Nervous and mental influences or any cause which affects the general metabolism may so change the character of the secretion in women as to make it no longer fit for the child. Violent emotion or shock have been known to lead to the complete suppression of the mammary secretion.[2] The employment of certain drugs also influences it. Thus atropine, if given in sufficient quantities, stops the secretion altogether, or if supplied in smaller amounts causes the milk to become more concentrated.

The occurrence of menstruation in women, or of heat in certain animals, may have a deleterious influence upon the milk, and so upon the offspring (see p. 362). In the case of cows, œstrus generally has a marked effect on the milk-yield, which as a rule shows at first a perceptible diminution, followed usually at the next milking by a yield well above the average. The fat content is generally at first considerably reduced, but at the following milking is sometimes abnormally high, or may be still abnormally low. On the two or three days preceding the outward manifestations of heat, the fat content tends to be decidedly above the average.

Ovariotomy is stated to have a beneficial effect upon goat's milk, relieving it of the characteristic hircine odour, increasing the quantity of butter, casein, and phosphoric acid (though decreasing the lactose present), and producing a greater and more long-continued secretion.[3] The removal of the ovaries in cows may also tend to improve the quality of the milk, rendering it richer than when the animals have been some months pregnant.[4]

The advance of lactation may be accompanied by changes both in the amount and in the composition of the mammary secretion, but the changes vary greatly in different individuals. In cows, the milk fat secreted in the first few days after parturition is poor in volatile acids, but it tends to improve rapidly during the first few months, the improvement being maintained until near the close of the lactation period, *i.e.* in most cases near the approach of the next parturition.[1]

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[1] Crowther, *loc. cit.*

[2] Williams, *loc. cit.*

[3] Oceanu and Babes, "Les Effets Physiologiques de l'Ovariotomie," *C. R. de l'Acad. des Sciences*, vol. cxl., 1905.

[4] Wallace, *loc. cit.*

It is well known that there is a change in the amount of milk produced by a cow as it grows older. Pearl has dealt with this matter statistically and has arrived at the following general conclusion: "The amount of milk produced by a cow in a given unit of time (seven days, one year, etc.) is a logarithmic function of the age of the cow."

The law may be stated verbally in the following way: Milk flow increases with increasing age but at a constantly diminishing rate (the increase in any given time being inversely proportional to the total amount of flow already attained) until a maximum flow is reached. After the age of maximum flow is passed the flow diminishes with advancing age and at an increasing rate. The rate of decrease after the maximum is, on the whole, much slower than the rate of increase preceding the maximum. In general the law above stated applies to the absolute amount of fat produced in a unit time as well as to the milk.[2] These conclusions agree with those of Gavin.

THE DURATION OF LACTATION

The duration of the lactation or nursing period in the different species of animals is governed mainly by the needs of the young. In such animals as the guinea-pig, in which the young are born in a sufficiently advanced state of development that they are able to fend for themselves, the length of the lactation period is relatively short and inconstant, while in other animals, belonging to the same order of Mammals, the young are born helpless, and are dependent for some weeks upon their mother's milk. In the larger animals the period of nursing is of course longer, but in them also its average duration appears to depend largely upon the necessities of the offspring.

The natural period of lactation in the cow is between nine and ten months, allowing for an interval of from two to three months to prepare for the next milking period. The duration of the period in any given animal depends to some extent upon such factors as diet and general treatment as described above, but there is much individual variation. Some cows continue to give milk until the next calving, but without a rest they are liable to yield a less abundant supply in the succeeding year.[1] Gavin[2] shows that in the absence of gestation the average milk yield falls from the maximum to about forty-five per cent. forty-two weeks after calving. One cow, however, was sold in milk sixty-three weeks after calving. If gestation intervenes the lactation-time is on the average very much shorter. The milk yield begins to drop about nine weeks after service, and once the reduction begins the rate of fall is steady.

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[1] In cows which are "drying off," the percentage of volatile acids in the butter fat is very low. See Crowther, *loc. cit.*

[2] Pearl, "On the Law Relating Milk Flow to Age in Dairy Cattle," *Proc. Soc. Exp. Biol. and Med.*, vol. xii., 1914. See also Pearl, "The Change of Milk Flow with Age," *Agric. Exp. State Papers*, Orono, Maine, 1917; and Gowen, "Studies in Milk Secretion," V. and VI., *Genetics*, vol. v., 1920. These papers give numerous references. For further information about variation in quantity and quality in milk of dairy cattle see papers by Pearl and by Gowen, *Jour. of Agric. Research*, vols. xvi. and xvii., 1919, and Gowen, *Jour. of Dairy Science*, vol. iii., 1920. For "Transmission or Inheritance of Milking Capacity" see Gowen, *Jour. of Heredity*, vol. xi., 1920.

It follows that a new gestation period in the cow has no arresting influence over the mammary secretion. Cows which have been castrated during lactation may yield milk for years without any cessation, and thus give on the aggregate a larger supply than cows which calve annually in the ordinary way. It is well known that constant milking acts as a stimulus to the secretory activity, and that cows which are not milked soon "run dry."

In the human female a year may be regarded as the normal period of nursing, any longer time involving what is known as hyperlactation. The practice of hyperlactation is said to be common, but it is to be deprecated in the interests of the infant.[3] It would appear that if continuous suckling is encouraged, the supply of milk in strong, healthy women may last almost indefinitely. As already mentioned, menstruation not infrequently commences to recur during the lactation period, and the latter may overlap gestation until within a short time of delivery.

THE DISCHARGE OF MILK

The discharge of the milk from the lactiferous ducts which occurs during sucking is due partly to the direct mechanical pressure, and partly to the action of the muscular tissue which is present in the walls of the ducts and in the nipple. The muscular mechanism appears to be stimulated reflexly by the action of sucking. The contraction of the muscles in the nipple causes this structure to stiffen, and it is suggested that this action has the effect of keeping open the orifices of the ducts, and thus permitting the free outflow of milk.[1]

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[1] Wallace, *loc. cit.*

[2] Gavin, "Studies in Milk Records," I., *Jour. Agric. Science*, vol. v., 1913. Gavin's results were obtained from a study of the data accumulated by the late Lord Rayleigh and the Hon. E. G. Strutt at Terling for twenty years.

[3] Dingwall Fordyce, "An Investigation into the Complications and Disabilities of Prolonged Lactation, etc.," an extension of papers published in the *Lancet*, the *British Medical Journal*, and the *British Journal of Children's Diseases*, 1906.

It is probable also that the discharge of the secretion is assisted in some degree by the swelling of the entire mammary gland resulting from a reflex dilatation of the vessels; but if the secretory process is very active, and the ducts are heavily charged, the flow of milk may take place almost automatically, and with hardly any external stimulus.

THE FORMATION OF THE ORGANIC CONSTITUENTS OF MILK

The principal organic constituents of milk are peculiar to the secretion, a fact which shows that they are elaborated in the mammary glands themselves, and not elsewhere in the body. It is stated, however, that a relatively small amount of caseinogen is present in the secretion of the sebaceous glands, from which, as already remarked, it is commonly supposed that the mammary glands[2] have been derived in the course of evolution. Nothing appears to be known definitely regarding the method of formation of the caseinogen of milk,[3] but it has been suggested that it is derived from the degenerate nuclei of the gland-cells.

The precise method by which the milk fat is formed is likewise unknown. It may be derived from protein material, the change being effected in the cells of the gland, or some of it may possibly have its source in fat which has already been formed elsewhere, and carried to the mammary glands in the blood or lymph. There is no reason for supposing that the cells of the glands do not possess, in common with most other tissues, the power to elaborate fat. On the other hand, there is definite histological evidence that they have this capacity (see above, p. 593). Moreover, the special composition of the milk fat seems to be by itself conclusive evidence that it is constructed within the mammary glands.

The suggestion has been made that the leucocytes which migrate through the epithelium and make their way into the secretory fluid may help to bring fatty globules into it,[4] but there seems no necessity for assuming that this is the case.

The fat formation which takes place in the cells of the lacteal glands in the process of milk manufacture has been compared with the fatty degeneration which occurs in other tissues, milk being nothing more than an emulsion of the fat of butter in a solution of salts, proteins, and sugar. "What occurs as a normal process in the cells of the lacteal glands occurs under pathological conditions in much greater extent in very various tissues, and leads almost always to incurable and fatal losses, since as a rule no reparation is made by the younger cells."[1] "The production of milk," says Virchow,[2] "in the brain instead of in the lacteal glands, constitutes a form of brain softening. The same process that in the one place affords the happiest and sweetest results, in another induces a painful and bitter wound." It has already been mentioned, however, that the fat of milk has a special composition of its own, so that too much stress must not be laid upon a resemblance between the secretion of milk and the pathological formation of other fluid substances in different parts of the body.

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[1] Sharpey Schafer, *loc. cit.*

[2] Neumeister, *Lehrbuch der physiologischen Chemie*, vol. ii., Jena, 1895.

[3] Thierfelder, "Zur Physiologie der Milchbildung," *Pflüger's Arch.*, vol. xxxii., 1883.

[4] Michaelis, "Beiträge zur Kenntniss der Milchsecretion," *Arch. f. Mikr. Anat.*, vol. xxi., 1898.

The mode of formation of the sugar of milk has been the subject of some controversy. Bert[3] supposed that it was formed from glucose which was absorbed by the cells of the mammary gland from the circulating blood. The glucose, according to this view, was manufactured in the liver, or, at any rate, elsewhere than in the mammary gland. Bert based his hypothesis upon two experiments in which the glands were removed from goats which afterwards became pregnant. The urine of each animal was tested during pregnancy to see if any reducing agent was present, but no such substance could be found prior to the birth of the kid. On the other hand, for several days after parturition a substance which reduced cupric sulphate was discovered in each case. Bert concluded that this was glucose. He supposed further that the reducing body present in the urine of the two goats represented glucose which in normal animals would have been converted into lactose in the mammary glands. The experiments were afterwards repeated by Moore and Parker,[4] who operated likewise upon two goats, and obtained results which were the direct opposite of those of Bert. These authors consequently concluded that the complete process of lactose formation takes place in the cells of the mammary glands.

The question was subsequently reopened by Porcher,[5] who also repeated Bert's original experiment on a goat. After parturition in the operated animal, an intense glycosuria is said to have occurred, the phenylhydrazine test showing that the substance present in the urine was glucose, and not lactose or some other reducing body. Porcher also removed the mammary glands from four goats and one cow during lactation, and for a few hours after the operation obtained marked glycosuria. As a result of these experiments, taken in conjunction with those of Bert, he concluded that the truth of the latter's theory was established beyond all doubt.

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[1] Verworn, *General Physiology*, Lee's Translation from the second German edition, London, 1899.

[2] Virchow, *loc. cit.*

[3] Bert, "Sur l'Origine du Sucre du Lait," *C. R. de l'Acad. des Sciences*, vol. lxxxviii., 1884.

[4] Moore (B.) and Parker, "A Study of the Effects of Complete Removal of the Mammary Glands in Relationship to Lactose Formation," *Amer. Jour. of Physiol.*, vol. iv., 1900.

[5] Porcher, "Sur l'Origine du Lactose," *C. R. de l'Acad. des Sciences*, vol. cxxxviii., 1904. "De la Lactosurie," *Monographies Cliniques*, Paris, 1906.

More recently the writer, working in conjunction with Dr. Kirkness,[1] carried out a series of experiments upon guinea-pigs. The mammary glands were removed prior to pregnancy (four cases) or during pregnancy (one case). The urine was tested for sugar both before and after parturition, but none was found in any of the experiments. Other experiments showed that glycosuria may occur after parturition in normal unoperated animals, but that it does not do so invariably.[2] When glycosuria does so take place, its occurrence is probably comparable to post-operative glycosuria, the cause of which is not understood. The glycosuria observed by Porcher after the removal of the mammary glands during lactation may perhaps be explained as an ordinary post-operative effect, and cannot be cited as proof of Bert's hypothesis.

According to Thierfelder[3] and Landwehr,[4] a formation of lactose may take place if pieces of fresh mammary tissue are kept in normal salt solution at body temperature. The lactose is said to be formed from a precursor which Landwehr identified as "animal gum" or carbohydrate of low reducing power.

According to Foà, there is a diminution of glucose in the venous blood coming from the mammary glands, but the amount of glucose and other carbohydrates present in the blood during lactation is no greater than in normal blood.[5]

Muntz[6] has put forward the view that the lactose of the mammary secretion is formed by the union of glucose, the normal sugar of the organism, with galactose, which is supposed to be derived directly by hydrolysis from certain polysaccharide substances introduced in the food. It is pointed out further, that such substances are present in plants which form the normal diet of certain animals. It would appear, however, that there is no direct evidence that lactose is actually formed in this way. Moreover, this theory can scarcely be applied to carnivorous animals, as Porcher[1] has pointed out.

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[1] Marshall and Kirkness, "On the Formation of Lactose," *Biochem. Jour.*, vol. ii., 1906.

[2] Puerperal glycosuria and lactosuria have been described in women in a number of cases. Lactosuria is also stated to occur not infrequently in the late stages of pregnancy both in women and animals, the lactose in such cases being presumably derived from the mammary glands by a process of absorption. So similarly lactose has been found in the urine of cows having accessory glands and teats from which the milk is not drawn off (see above, p. 587; Mackenzie and Marshall, MS. unpublished). See Hofmeister, "Ueber Laktosurie," *Zeitsch. f. physiol. Chem.*, vol. i., 1887; Porcher, *De la Lactosurie*, 1906; and "L'Origine du Lactose," *Arch. Internat. de Phys.*, vol. viii., 1909. See also p. 539.

[3] Thierfelder, "Zur Physiologie der Milchbildung," *Pflüger's Arch.*, vol. xxxii., 1883.

[4] Landwehr, "Ueber die Bedeutung des tierischen Gummis," *Pflüger's Arch.*, vol. xl., 1887.

[5] Foà, "Sull' Origine del Lattosio del Latte," *Arch. di Fis.*, vol. v., 1908.

[6] Muntz, "Sur l'Existence des Éléments du Sucre de Lait dans les Plantes," *Annales de Chim. et de Phys.*, vol. x.

There is, therefore, no definite evidence that lactose is elaborated in the mammary glands from any closely related carbohydrate precursor carried thither from elsewhere in the body. It is more likely, as Hammond has suggested, that milk-sugar is derived from a glycoprotein precursor which, mixing with water and salts from the blood, contributes to the secretory product. As evidence of this contention he refers to a number of experimental observations by different physiologists besides recording a series of experiments of his own. The evidence is summarised in the next paragraphs.

Lusk[2] states that after administering phloridzin (which removes glucose from the blood by causing it to be excreted in the urine) to a goat the results were a reduction in the milk yield but an increase in the percentage of fat. Similarly Porcher,[3] experimenting on cows and goats, obtained a reduction in the milk yield. Paton and Cathcart,[4] by injecting phloridzin, likewise produced a decrease in the secretion together with a diminution in the lactose, nitrogen, and ash. When the milk secretion was most reduced the sugar excreted in the urine was greatest. Rose[5] found that the milk secreted varied inversely with the phytin in the food, and that when the latter was increased the percentage of fat in the milk increased.

Hammond[6] himself found that as a result of injecting pituitary extract, which acts as a powerful immediate galactogogue (see below, p. 621), the milk was normal in composition except for an increase in the fat. (The daily yield was only slightly increased; thus if the goat was injected in the morning the milk secreted at that time was greatly increased, but the evening milk was reduced almost in proportion.) The ratio of nitrogen to lactose in the milk was almost constant throughout.

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[1] Porcher, "Sur la Physiologie de la Mamelle," *Jour. de Méd. Vet. de l'École de Lyon*, 30th September 1905.

[2] Lusk, "Ueber Phloridzin-Diabetes," *Zeitsch. f. Biol.* (Festschr. B. Voit), 1901.

[3] Porcher, "L'Origine du Lactose," *Arch. Internat. de Phys.*, vol. viii., 1909.

[4] Paton and Cathcart, "On the Mode of Production of Lactose in the Mammary Gland," *Jour. of Physiol.*, vol. xlii., 1911.

[5] Rose, "A Study of the Metabolism Effects of Certain Phosphorous Compounds," New York State, *State Tech. Bull.*, 1912.

[6] Hammond, "The Effect of Pituitary Extract on the Secretion of Milk," *Quart. Jour. Exp. Physiol.*, vol. vi., 1913. Hammond and Hawk, "Studies in Milk Secretion," *Jour. Agric. Science*, vol. viii., 1917.

As a result of withholding food for a few days, together with an injection of phloridzin, thereby considerably reducing the nutrition, the yield of milk could be greatly diminished but the fat percentage rose. The fat, however, subsequently diminished, possibly as a secondary effect of the decreased secretion by the gland-cells. On feeding such animals the milk yield rapidly increased, but the percentage of fat decreased. Hammond found also that the amount of milk produced by the action of pituitary extract varied with the state of nutrition, and he concludes that the fat percentage of the pituitary milk is increased by a condition of lowered nutrition in the same way as with normal milk. Further, after injecting adrenalin the fat percentage in the milk is increased but the actual quantity of milk is somewhat below the normal.

Taylor and Husband,[1] as a result of a recent investigation upon cow's milk, have reached the following conclusions: The percentage composition of the milk seems to be determined by its rate of secretion. The percentages of protein and ash, as well as of fat, vary inversely, and the percentage of lactose varies directly, as the daily volume, the greatest variation being shown by the fat and the least by the inorganic elements. There is an inverse relationship between the percentage of lactose and the percentages of all the other constituents of the milk, this being particularly apparent in the case of the fat. Diet has no direct influence on the percentage composition of the milk, except in the case of the non-protein nitrogen which is not a product of the mammary gland. Diet has, however, an indirect influence by reason of its effect on the daily volume. A high protein diet would appear to stimulate the rate of secretion of the milk. It is suggested, further, that the quantity of lactose elaborated by the gland may control the daily volume of milk, and that therefore the rate of its elaboration is a regulative factor in the rate of milk secretion.

THE NORMAL GROWTH OF THE MAMMARY GLANDS

The growth of the mammary glands in the rabbit has been described by Miss Lane-Claypon and Starling, from whose paper the following account is taken.[2]

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[1] Taylor and Husband, "The Effect on the Percentage Composition of the Milk of (*a*) Variations in the Daily Volume, and (*b*) Variations in the Nature of the Diet," *Jour. of Agric. Science*, vol. xii., 1922. This paper contains further references.

[2] Lane-Claypon and Starling, "An Experimental Inquiry into the Factors which Determine the Growth and Activity of the Mammary Glands," *Proc. Roy. Soc.*, B., vol. lxxvii., 1906. See also Brouha, *loc. cit.*

In the virgin animal of about eight to twelve months old mammary tissue cannot ordinarily be detected with the naked eye, but in stained preparations of the connective tissue surrounding the nipple, it is possible to see the ducts which comprise the gland. These are generally restricted to an area of not more than one centimetre broad. Sections show that the gland at this stage consists entirely of ducts which are lined with a single layer of flattened epithelium, and end blindly. No traces of alveoli are to be seen in the gland.

By the fifth day after conception a marked change has taken place in the gland, which now appears, on reflecting the skin from the abdomen, as a clearly differentiated pink area, circular in shape, and surrounding the position of each nipple. The diameter of this area is from about two to three centimetres. Sections through the gland show that it still consists entirely of ducts, but that these are in a state of active proliferation. The epithelial lining no longer consists of a single cellular layer, but is two or three cells deep, while the individual cells are more swollen than those of the virgin gland, and mitotic figures are commonly seen.

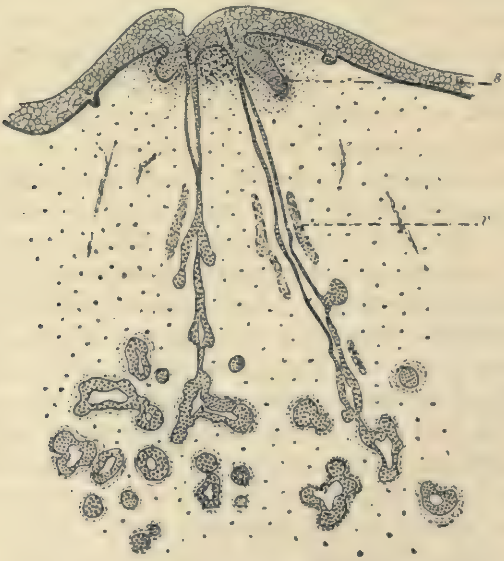

FIG. 166.—Section of developing mammary gland of horse. (From Sharpey Schafer, after Hamburger.)

s, Sebaceous glands ; *v*, blood-vessels.

The mammary gland now grows rapidly, so that on about the ninth day after conception, on reflecting the skin from the abdomen, the entire surface is found to be covered with a layer of glandular tissue, the margins of the individual glands being practically contiguous, each of them having a diameter of from five to eight centimetres. Sections show that the formation of alveoli (*i.e.* definite secretory structures) has begun at this period, especially at the periphery, where the gland is generally somewhat thicker than in other parts.

From this stage onwards the growth of the ducts and the formation of alveoli proceed rapidly, so that by the twenty-fifth day of pregnancy the whole surface of the abdomen has become covered by mammary gland tissue, which may be half a centimetre thick. This tissue is seen in sections to consist for the most part of alveoli, in the cells of which fat globules are in process of formation.

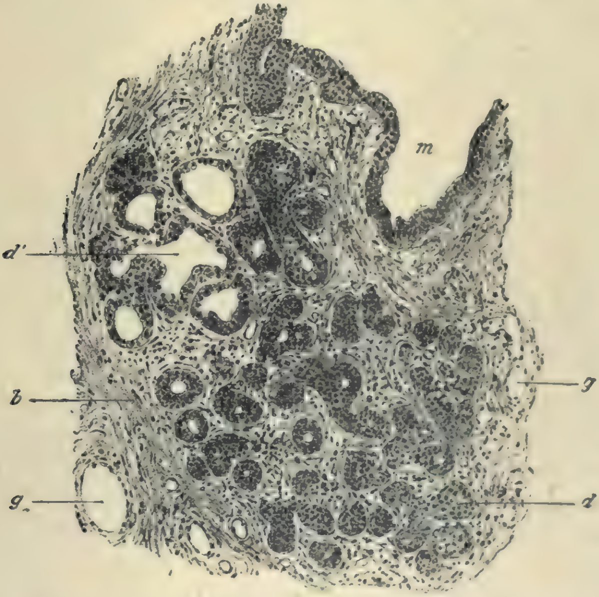

FIG. 167.—Section of mammary gland (human), showing developing alveoli. (From Sharpey Schafer, after von Ebner.)

b, Connective tissue ; *d*, undeveloped alveoli ; *d′*, partially developed alveoli ; *g*, blood-vessel ; *m*, portion of duct.

From about the ninth day onwards to the twenty-fifth it is usually possible to squeeze a watery fluid from the nipples. During the last days of pregnancy this fluid assumes the characteristics of normal milk, so that by the time of parturition, which occurs in the rabbit on the thirtieth day after conception, the glands are full of milk.

The multiparous rabbit differs from the virgin in possessing ready-formed alveoli at the beginning of pregnancy. Consequently the amount of mammary growth during the gestation period of the multiparous animal is relatively less.

The changes which take place in the human female and in other animals during pregnancy are in a general way similar to those occurring in the rabbit. In women after the second month the breasts are said to offer a nodular sensation on palpation, this being due to the hypertrophy of the mammary alveoli. The nipples also enlarge, and at the same time become more erectile and pigmented, while the areola surmounting the nipple becomes broader and pigmented also, in dark individuals being often almost black. The hypertrophy of the sebaceous glands in the areola results in the formation of the so-called glands of Montgomery, which appear as small round elevations. As already mentioned, during the later months of pregnancy the thin yellowish fluid known as colostrum can generally be expressed from the nipples.

The mammary glands are said to undergo growth at puberty, and there can be no doubt that a slight hypertrophy generally takes place in connection with each period of procestrum and œstrus. These changes must be ascribed to ovarian influence, which, as has already been proved, is responsible for the changes which occur at such times in the other generative organs, while, as shown below, the mammary growth which takes place after ovulation is due to the corpus luteum. Gellhorn[1] refers to a case of a woman who had abnormal mammary glands with seven nipples in the neighbourhood of the mons veneris, and who yielded milk at each menstrual period. Other similar cases have been recorded. This phenomenon is, of course, contrary to the more usual tendency for menstruation to be in abeyance during lactation.

THE FACTORS WHICH ARE CONCERNED IN THE PROCESSES OF MAMMARY GROWTH AND SECRETION

It has just been mentioned that the mammary glands in the female begin to undergo enlargement at the period of puberty in correlation with the increase in ovarian activity. In man the difference between the glands in the two sexes is first manifested at this time. The slight hypertrophy which occurs in connection with each proœstrous period has been referred to, while the great growth which the glands undergo during pregnancy has also been described.

It was formerly supposed that there was a direct reflex connection between the growth of the mammary glands and the development of the embryo in the uterus, the hypertrophy of the glands being determined through the intermediation of the central nervous system. There is now, however, abundant evidence that such is not the case. This is shown, for example, by the experiment performed by Goltz and Ewald,[1] which has already been referred to in considering the factors concerned in parturition. The lumbo-sacral part of the spinal cord was completely exsected in a pregnant bitch, so that all possible connection between the mammary glands and pelvic organs through the nervous system was destroyed. Pregnancy was accompanied as usual by mammary development, and after parturition, lactation occurred normally. Routh's case,[2] in which normal lactation took place in a woman with complete paraplegia below the level of the sixth dorsal vertebra, has also been referred to (p. 571). Moreover, it has been shown by Eckhard[3] that after complete severance of the nerves (branches of the external spermatic) passing to the mammary gland, the activity of the latter, and consequently the supply of milk, are in no way affected.[4]

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[1] Gellhorn, "Abnormal Mammary Secretion," *Jour. Amer. Med. Assoc.*, 21st November 1908.

Further evidence in support of the conclusion that the connection between mammary and fœtal growth is not nervous in character is supplied by those experiments in which portions of gland were successfully transplanted to abnormal positions in the body. Thus in an experiment on a guinea-pig Ribbert[5] grafted mammary tissue from the normal position to the neighbourhood of one of the ears.

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[1] See pp. 514 and 571.

[2] Routh, "Parturition during Paraplegia, with Cases," *Trans. Obstet. Soc.*, vol. xxxix., 1897.

[3] Eckhard, *Beiträge zur Anat. u. Phys.*, vol. i., Giessen, 1855.

[4] Eckhard's experiments have been repeated by others with somewhat contradictory results (see Basch, *loc. cit.*); Röhrig ("Experimentelle Untersuchungen über die Physiologie der Milchabsonderung," *Virchow's Archiv*, vol. lxvii., 1876) found that the external spermatic nerve contained vasomotor fibres for the vessels of the mammary gland, and that these affected its secretory activity by controlling the blood supply. Mironow ("De l'Influence du Système Nerveux des Glandes Mammaires," *Arch. des Sciences Biol. de St. Petersbourg*, vol. iii., 1894) states that artificial stimulation causes a reduction in the quantity of secretion. He states further that whereas section of the external spermatic on one side has no effect on the secretion, section on both sides diminishes it, but that the diminution only comes on gradually after a number of days. After complete severance of all the nerves in pregnant animals the glands may continue to grow and yield milk after parturition. Basch (*loc. cit.*) states that extirpation of the cœliac ganglion or transection of the spermatic nerve does not inhibit the secretory process, but increases the number of colostrum corpuscles. There is abundant evidence of a general kind that the central nervous system in some way exerts an influence on the mammary gland. Thus the effects of nervous shock in altering or inhibiting milk secretion in women are well known. Moreover, the occurrence of uterine contractions on putting the child to the breast, and so stimulating the nipples, is evidence of a nervous connection. It would seem probable, therefore, that though the mammary gland is essentially an automatic organ, the connection of which with the generative organs is through the vascular rather than the nervous system, yet it is under the regulating control of the latter by means of secretory or vasomotor fibres.

[5] Ribbert, "Ueber Transplantation von Ovarium, Hoden und Mamma," *Arch. f. Entwick.-Mechanik*, vol. vii., 1898.

Notwithstanding the fact that the transplanted gland had lost its normal nervous connections, it underwent enlargement during a subsequent pregnancy, and afterwards secreted milk. Pfister[1] states that he performed a similar experiment on a rabbit, and obtained a similar result.

The inference is, therefore, that the relation between the growth of the mammary glands and the development of the fœtus in the uterus is chemical in nature.

Lombroso and Bolaffio[2] have described an experiment in which two female rats were grafted together so that their respective circulatory systems were presumably united. Subsequently to their union they each became pregnant, but at different times. They afterwards produced young, one prematurely, and the other at full term. The mammary glands of each underwent the characteristic changes, but they occurred independently and not synchronously. The authors cite this result as evidence against the fœtal hormone theory. Moreover, as a result of this and another similar experiment, they conclude that parturition is not induced by a chemical excitant circulating in the blood (see p. 574).

On the other hand, in the case of the Bohemian pygopagous twins, Rosa-Josepha, the mammary glands of both are described as having been similarly and simultaneously affected by the pregnancy of Rosa, who bore a healthy boy on April 17, 1910. Milk was afterwards secreted by the breasts of Josepha as well as of Rosa, although Josepha had never conceived.[3]

As Miss Lane-Claypon and Starling have pointed out, the phenomenon of fertilisation succeeded by fœtal growth involves the occurrence of changes in the ovaries and in the uterus (both in the muscle and in the mucous membrane), as well as the formation of an organ of complicated structure—the placenta—the function of which is to nourish the developing young. The question arose, therefore, as to whether the fœtus or either of the above-mentioned organs was not the direct source of formation of a hormone or chemical excitant which, after circulating in the blood-stream, acted as a stimulus to mammary growth.

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[1] Pfister, "Ueber die reflektorischen Beziehungen zwischen Mammæ und Genitalia muliebria," *Beiträge zur Geb. und Gynäk.*, vol. v., 1901.

[2] Lombroso and Bolaffio, "La Parabiosi e la Questione dei Fattori che determinano la Fuz Funzione mammaria e l'Insorgenza del travaglio di parto," *Atti della Soc. Ital. di Obstet. e. Gin.*, vol. xv., 1909.

[3] *British Med. Jour.*, Part II., 28th May 1910. The twins were described as being united posteriorly by a common sacrum, but the iliac bones were separate. There was a common anus, perineum, clitoris, and meatus urinarius, but the labia majora were double. The urethra was single for an inch above the meatus, but then it bifurcated. The ureters were normal. The desire to micturate was said to be distinct, but not the desire to defæcate. The twins died at the same time in April 1922.

It has been shown that milk can be secreted if the ovaries are removed in the latter part of pregnancy, but it is not clear whether the secretion begins immediately after ovariotomy or whether it is postponed till after parturition.[1]

It is known that the mammary glands undergo normal development in cases of extra-uterine fœtation in which the growth of the uterus is relatively small. This observation clearly indicates that the source of the stimulus in question is not to be sought in the hypertrophied uterus. A consideration of these and other facts led Miss Lane-Claypon and Starling to the conclusion that one or other of the products of conception (*i.e.* either the fœtus or placenta), or possibly both, were the seat of origin of the specific chemical stimulus which brought about mammary growth.

Halban[2] had recently formed the opinion, chiefly on clinical grounds, that the specific stimulus arose mainly in the chorionic villi and placenta.

Ancel and Bouin have suggested that the stimulus for mammary growth in the later part of pregnancy is produced by the so-called myometrial gland which is said to be located in the muscular layers of the uterus, but according to other observers there is no evidence for this suggestion (see below, p. 618).

The Fœtal Hormone Theory.—Miss Lane-Claypon and Starling appear to have been the first to deal with the problem experimentally. In an initial series of experiments they injected extracts or emulsions of ovaries obtained from pregnant rabbits into other rabbits either subcutaneously or intraperitoneally. In two further series of experiments rabbits were injected with uterine and placental emulsions or extracts. In no case, however, did the injections produce any effect on the mammary glands, although in certain of the experiments in which ovarian or uterine substance was employed, marked swelling and congestion of the uterus were afterwards observed.

The effect of injecting fœtal extract was next tried, and this led apparently to positive results. When repeatedly injected into female rabbits the extract seemed to produce a genuine development of the mammary glands which simulated the normal growth which occurs during pregnancy. In one case a virgin rabbit received fifteen injections of extract made from many embryos of the same species. The injections were spread over a fortnight, at the end of which the rabbit was killed. It was found that a secretory fluid could be expressed from the nipples, and that on reflecting the abdominal skin all the mammary glands had grown to the size which is ordinarily reached in a rabbit about eight days pregnant. In another rabbit which received twenty-four injections, spread over five and a half weeks, the effects produced were still more marked. Further experiments showed that boiled extract was as effective as unboiled, and the conclusion was therefore drawn that in all probability the specific secretion or hormone is capable of withstanding boiling. It was shown also that the substance in question could be obtained equally well from different parts of the fœtus, that it passes through a Berkefeld filter, and that it is not retained to any appreciable extent by the kieselguhr in Buchner's method for extracting cell juices.

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[1] Marshall and Jolly, "Contributions, etc.," *Phil. Trans.*, B., vol. cxcviii., 1905.

[2] Halban, "Die innere Sekretion von Ovarium und Placenta und ihre Bedeutung für die Function der Milchdrüse," *Arch. f. Gynäk.*, vol. lxxv., 1905.

Foà states that extract of ox fœtus, when injected into rabbits, produced development of the mammary glands. He concluded, therefore, that the stimulating substance which causes mammary growth is not specific—*i.e.* not peculiar to any one kind of mammal. Foà says also that if the extract is heated to 110° the active substance is destroyed, and no result is produced by injection.[1]

Since the growth of the mammary glands was apparently due to a specific chemical stimulus arising in the fœtus, it was natural to suppose that the beginning of the actual secretory process which marks the cessation of growth was caused by the removal of this stimulus—in other words, by the expulsion of the fœtus. In this connection it is interesting to note that abortion or premature labour is often followed by the appearance of milk in the breasts.

The idea that lactation is due to the removal of an inhibition appears to have been entertained first by Hildebrandt,[2] who put forward the suggestion that the developing embryo exerts an influence whereby the cells of the mammary gland are protected from those autolytic disintegrative processes which are supposed to occur during active secretion. That the act of secretion is to be ascribed to autolytic processes of the gland, is, according to Miss Lane-Claypon and Starling, highly improbable, and there is no evidence that the autolysis of the gland-cells would give rise to the specific constituents which characterise milk.

Halban[3] has put forward the view that the specific stimulus for mammary development arises in the placenta, while the active secretion of the mammary glands is determined by the expulsion or death of the placenta.[1] Keiffer,[2] on the other hand, has entertained the contrary conception, that the secretion of milk is due to a ferment elaborated in the placenta and transferred to the maternal circulation at the time of birth. These theories are based mainly on clinical evidence of a somewhat questionable value.

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[1] Foà, "Sui Fattori che determinano l'Accrescimento e la Funzione della Ghiandola Mammaria," *Arch. di Fis.*, vol. v., 1908.

[2] Hildebrandt, "Die Lehre von der Milchbildung," *Hofmeister's Beiträge*, vol. v., 1904.

[3] Halban, *loc. cit.* See also Bouchacourt, *C. R. de la Soc. de Biol.*, 1902; and Lederer and Przibram, *Pflüger's Arch.*, vol. cxliv., 1910. The latter authors found that extract of placenta injected into a goat caused a marked increase in milk, while ovarian extract had no effect.

According to Miss Lane-Claypon and Starling's experiments, after multiparous rabbits are injected with fœtal extract milk is secreted by the glands. This result was explained as follows: "The multiparous rabbit differs from a virgin rabbit in possessing ready-formed alveoli, *i.e.* secretory structures. On the theory which we have adopted, the circulation of the mammary hormone should diminish any secretion in these alveoli, and should cause growth. In all our experiments at least twenty-four hours elapsed between each two injections. It is probable that the hormone was rapidly absorbed from the injection, and was therefore present in the blood of the animal only for a certain fraction, say a few hours, out of the twenty-four. While it was circulating it should cause building up of the secreting cells. Directly, however, it ceased to circulate, the cells would enter into dissimulative activity resulting in secretion. By our injections, therefore, we are not able to imitate the continuous stimulus of pregnancy. We are rather producing each day a pregnancy of a few hours followed by a parturition. These factors should therefore result in the production of milk in any animals possessing the structures (*i.e.* the alveoli) which are capable of secreting milk, and would therefore account for the secretion of milk observed by us in all the cases where multiparous rabbits were the objects of our experiment."

It has been shown that in the fœtus itself there is an increased growth of the mammary glands during the last part of pregnancy, while it is well known that a secretion is often formed in the glands of the newly born. Halban has explained this secretion as the result of removal of the inhibitory influence—that is to say, it is due to the same circumstance as the secretion in the mother. Miss Lane-Claypon and Starling point out that the complete change which occurs in the environment of the newly-born animal must induce equally profound changes in the metabolism, and there is consequently no difficulty about the conclusion that the formation of the mammary hormone ceases with the commencement of extra-uterine life.

The general conclusions at one time reached by these authors may be summarised as follows: The anabolic changes associated with the growth of the mammary glands are due to the assimilatory effects of a hormone elaborated in the fœtus and carried thence through the placenta by the fœtal and maternal circulation. The removal of this stimulus produces those katabolic changes which are involved in the breaking down of the built-up tissues and the consequent formation of milk.[1]

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[1] He points out that in cases of abortion the secretion of milk may not begin until some days after the death of the child. This he believes to be due to the circumstance that the placenta remains alive during the interval.

[2] Keiffer, "Recherches sur l'Anatomie et la Physiologie de la Mamelle," *Bull. de la Soc. Belge de Gyn. et d'Obstét.*, 1901-02.

In criticism of these conclusions, which, however, the authors never regarded as more than tentatively established, certain objections were urged. It was pointed out that in certain animals the period of lactation may continue for an almost indefinitely long time, so that it would appear as if the katabolic processes involved in milk-secretion were out of all proportion to the anabolic processes concerned in the building up of the gland tissue. For example, it is stated that in castrated cows the mammary glands may remain perpetually active for years and years so long as milking is regularly continued (see p. 600). Moreover, in some animals (*e.g.* mares) a secretion of milk may be induced artificially as a result of a mechanical stimulus set up by repeated attempts at milking. In one instance known to the writer, a mare which had never had a foal could be made to yield milk at any time for years. It would seem probable, however, that in such cases there must have been an original tendency to secrete, and that this tendency was merely augmented by the emptying of the galactophorous ducts. This is in accordance with the view that the emptying of the ducts during normal suckling constitutes a physiological stimulus which acts on the gland-cells, either directly or by means of a reflex.

Heape[2] has pointed out as an objection to Starling's theory of the fœtal hormone that virgin bitches are frequently known to produce milk, and that the quantity secreted may even be sufficient to admit of their rearing pups. He also refers to a statement by Tegetmeier and Sutherland[3] that mules may yield milk in sufficient abundance to rear a foal. He concluded, therefore, that the source of the stimulus which excites the development of the mammary glands is to be sought in the ovary rather than in the fœtus.

Instances have also been recorded by Knott[4] and others, in which males have secreted milk, thus showing that mammary development is not necessarily even a female function; but such cases are at all events exceedingly rare.[1] Knott mentions cases in which suckling occurred in a bull, a male goat, a wether, and in men. He also cites instances of virgin girls who were nurses secreting copious supplies of milk as a consequence of allowing infants to suck their nipples; and thus he supports Heape's objection to the fœtal hormone theory. Gellhorn[2] cites similar cases, including one of a virgin monkey (*Cercopithecus*). Another case is mentioned of a woman who suckled children uninterruptedly for forty-seven years, and in her eighty-first year had a moderate but regular supply of milk,[3] thus showing that mammary secretion may continue exceptionally for long after the menopause, and presumably, therefore, in the absence of any sort of stimulus from the generative organs. This observation further supports the idea referred to above, that normal suckling acts by itself as a physiological stimulus for mammary secretion.

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[1] According to Foà (*loc. cit.*) fœtal extract has no inhibitory influence on mammary secretion.

[2] Heape, "The Source of the Stimulus which causes the Development of the Mammary Gland and the Secretion of Milk," *Proc. Phys. Soc., Jour. of Physiol.*, vol. xxxiv., 1906.

[3] Tegetmeier and Sutherland, *Horses, Asses, Zebras, Mules, and Mule Breeding*, London, 1895.

[4] Knott, "Abnormal Lactation, etc.," *American Medicine*, vol. ii., (new series, June) 1907. *Cf.* Wiedersheim (see p. 587).

Halban[4] has remarked that the seat of the stimulus for milk secretion must be placed outside the fœtus, since parturition may result not only in the mother secreting but also the fœtus which produces the so-called "witch's milk." Again, cases are described in which a woman has produced a healthy, well developed child, and yet secreted very little milk.[5] O'Donoghue[6] has pointed out that the rabbit secretes milk several days before parturition, whereas man and *Dasyurus* do not do so until several hours after it. Moreover, Hammond[7] has recorded a case of a goat which secreted large amounts of milk (800 c.c. daily) for three weeks before parturition.

An equally forcible objection to the theory of the fœtal hormone is supplied by the Monotremata, which are the lowest order of Mammalia. These animals are oviparous, the developing embryo being contained in an egg, which does not enter into any sort of connection with the uterine wall. Halban,[8] however, has made the suggestion, which is quoted by Miss Lane-Claypon and Starling, that since the embryo goes on increasing in size during its passage down the female generative tract, and since the shell of the egg is porous, it is not impossible that substances may diffuse outward from the embryo and be absorbed by the uterine mucous membrane, and so be carried into the maternal circulation.

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[1] The occasional occurrence of milk secretion in the newly born, both males and females, is well known.

[2] Gellhorn, *loc. cit.*

[3] Knott, *loc. cit.*

[4] Halban, "Die innere Sekretion von Ovarium und Placenta," *Arch. f. Gyn.*, vol. lxxv., 1905.

[5] Hammond, "On the Causes Responsible for the Developmental Progress of the Mammary Glands in the Rabbit during the latter part of Pregnancy," *Proc. Roy. Soc.*, B., vol. lxxxix., 1917.

[6] O'Donoghue, "The Growth Changes in the Mammary Apparatus of *Dasyurus* and the relation of the Corpora Lutea thereto," *Quar. Jour. Micr. Science*, vol. lvii., 1911.

[7] Hammond, *loc. cit.*

[8] Halban, *loc. cit.*

Miss Lane-Claypon and Starling, however, never contended that the fœtus is the sole source of the stimulus for mammary development. On the other hand, they specially mentioned that the growth of the mammary glands which occurs at puberty, for instance, can only be attributed to ovarian influence, since it does not take place if the ovaries have been previously removed. It is not improbable, therefore, that an ovarian stimulus is also responsible for producing the growth of the glands in Monotremes, in just the same kind of way as has been demonstrated for other animals.

The fœtal hormone theory has now been superseded by the hypothesis of the corpus luteum as the main controlling factor in the growth of the mammary glands. Starling and Lane-Claypon, however, did useful service in emphasising the part played by the fœtus in promoting the growth of the glands in pregnancy, for it is only in the presence of the fœtus *in utero*, at any rate in placental Mammals, that the complete development of the glands followed by full lactation is normally attained.

The Corpus Luteum.—Ancel and Bouin[1] were the first to show that the growth of the mammary glands during the first part of pregnancy is due to the corpus luteum. Their researches were upon the rabbit which only ovulates after copulation (see p. 129), so that normally, since the discharged ova are fertilised, the presence of corpora lutea is always associated with pregnancy. Ancel and Bouin, however, by employing males in which the vasa deferentia had been severed, were able to induce the formation of corpora lutea without the occurrence of gestation. The same results can be brought about by severing the Fallopian tubes of the female or by removing the uterus, as was shown later by the present writer, working in conjunction with Mr. Hammond.[2] We described the condition produced as one of "pseudo-pregnancy," a name already used by Hill and O'Donoghue[3] to designate the similar state of functional correlation which occurs normally in the Marsupial cat (*Dasyurus viverrinus*) after spontaneous ovulation. These authors have shown that in *Dasyurus* the changes undergone by the mammary glands are identical whether pregnancy supervenes or not (see p. 36).

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[1] Ancel and Bouin, see references, p. 371. For a full account of the changes in the glands with many references to literature see Schil, *Recherches sur la Glande Mammaire*, Nancy, 1912.

[2] Hammond and Marshall, "The Functional Correlation between the Ovaries, Uterus, and Mammary Glands in the Rabbit," *Proc. Roy. Soc.*, B., vol. lxxxvii., 1914.

[3] Hill and O'Donoghue, "The Reproductive Cycle in the Marsupial Cat, *Dasyurus viverrinus*," *Quar. Jour. Micr. Science*, vol. lix., 1913.

There is always a hypertrophy followed by a secretion of milk, and superficially it is impossible to distinguish pseudo-pregnancy from true pregnancy. Moreover, in the dog,[1] which also ovulates spontaneously, pseudo-pregnancy may follow the discharge of the ova, the corpus luteum persisting and the mammary glands undergoing growth followed by secretion, a fact which explains the observations of Heape and others that even virgin bitches frequently lactate and are capable of suckling litters of pups produced by other individuals.

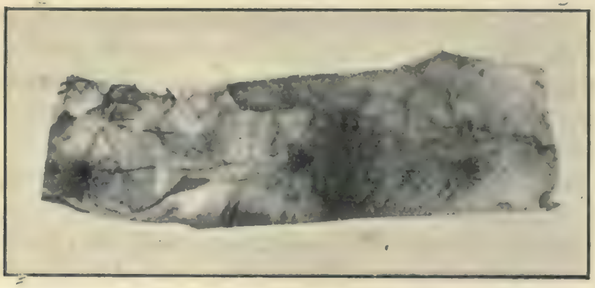

FIG. 168.—Photograph of mammary tissue of virgin rabbit. The mammary development is limited to a few ducts. (From Hammond and Marshall.)

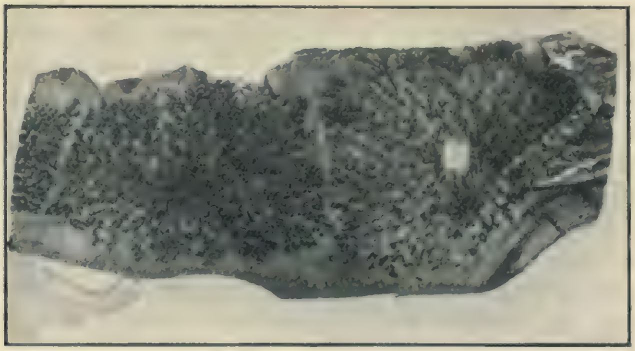

FIG. 169.—Photograph of mammary glands of pseudo-pregnant rabbit fourteen days after œstrus. The rabbit had never bred. (From Hammond and Marshall.)

The hypertrophy of the mammary glands in the pseudo-pregnant rabbit culminates at about the sixteenth day,after which time it begins to regress, but milk may be expressed from the nipples from the nineteenth day onwards for a week or so, and even in individuals which were previously virgins, while, as already mentioned, on about the eighteenth day the rabbit may display the instincts associated with parturition (see p. 576). In true pregnancy the milk glands still continue to grow, increasing in thickness and in weight until from the twenty-fourth to the thirtieth day, that is to say, until at or near the time of parturition.[1] The pseudo-pregnant condition thus differs from that of true pregnancy. Similarly in the pseudo-pregnant bitch the milk glands do not hypertrophy to the same extent as in the pregnant animal. In both species of Mammals the differences in mammary development are less marked in individuals which have previously borne young and in which consequently the mammary glands had already undergone a hypertrophy which was to a great extent persistent.

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[1] Marshall and Halnan, "On the Post-Œstrous Changes occurring in the Generative Organs and Mammary Glands of the Non-Pregnant Dog," *Proc. Roy. Soc.*, B., vol. lxxxix., 1917.

Ancel and Bouin[2] ascribe the growth of the milk glands in the later part of pregnancy to the myometrial gland, which is stated to consist of clumps of epithelioid cells lying under the placental cells and between the muscle cells of the longitudinal and circular coats in close proximity to the blood-vessels. They suggest that this gland is an organ of internal secretion which takes over the functions of the corpus luteum during the second half of pregnancy, controlling the later or "glandular" phase of the mammary gland as well as the tolerance of the uterus for the fœtus. Fraenkel[3] has confirmed the observations upon the presence of the myometrial gland in the rabbit but has failed to find it in other species examined. Mercier,[4] however, has identified the cells of the gland with certain phagocytic cells which he had previously found in the pregnant uterus. Hammond[5] says that they are not constant even in rabbits, and when present are probably fœtal cells which have wandered into the muscular coat.

As already mentioned, the placenta has also been suggested as a source of the stimulus for the mammary growth of pregnancy. Hammond, however, has eliminated this organ as a possible factor by causing decidual tissue to form through the stimulation of the uterus by a foreign body or by an incision after the manner of Loeb

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[1] Hammond, "On the Causes Responsible for the Developmental Progress of the Mammary Glands in the Rabbit in the latter part of Pregnancy," *Proc. Roy. Soc.*, B., vol. lxxxix., 1917.

[2] Ancel and Bouin, "Sur l'Existence d'un Glande Myométriale, etc.," *C. R. Assoc. des Anat.*, 13 Réunion, 1911; "Recherches sur les Fonctions du Corps jaune gestatif," *Jour. de Phys. et de Path. Gén.*, vol. xiii., 1911; "Sur l'Évolution de la Glande mammaire pendant la Gestation," *C. R. de la Soc. Biol.*, vol. lxxii., 1912. See also *C. R. de l'Acad. des Sciences*, vol. cliv., 1912.

[3] Fraenkel, "Untersuchungen über die Sogenannte Glande endocrine myométriale," *Arch. f. Gyn.*, vol. xcix., 1913.

[4] Mercier, "Sur l'Existence de Nephrophagocytes dans le Muscleuterin, etc.," *C. R. de la Soc. de Biol.*, vol. lxxii.; and other papers in vols. lxxiii. and lxxiv., 1912 and 1913.

[5] Hammond, *loc. cit.*

(p. 374), and then finding that the development of the glands was never in excess of what takes place under the influence of the corpora lutea of pseudo-pregnancy. Moreover, he found that in rabbits in which the fœtuses were removed but the placentas retained there were no secondary growth changes in the milk glands. Biedl and Koenigstein[1] had already shown that implantation of placenta was without effect on the glands but that transplantation of the fœtus resulted in mammary growth and the secretion of milk.

Hammond found also that, contrary to the generally accepted opinion, the corpus luteum in the rabbit is fully persistent and therefore active during the second half of pregnancy. This conclusion is based on a series of measurements of corpora lutea at different days after copulation in pregnant and pseudo-pregnant individuals, and in others in which decidual cells had been experimentally produced or in which the fœtuses had been removed. It was found that the corpora lutea, after the sixteenth day, retained their size only in pregnant rabbits and in these underwent some further development; in the other three series they underwent a very marked regression. Hammond concluded, therefore, that the development of the mammary glands of the rabbit during the second part of pregnancy is under the same influence as that which controls it during the first half, namely, the corpus luteum, and that the further development and persistence of the latter organ in the last part of gestation is due to the presence of the fœtus.

In the virgin rabbit, as already mentioned, the mammary tissue before ovulation is limited to a few small ducts in the immediate vicinity of the nipple, no true growth taking place until the corpus luteum begins to develop. In polyœstrous animals which ovulate spontaneously, on the other hand, notwithstanding the fact that they do not experience pseudo-pregnancy (excepting possibly in a very abbreviated form), mammary tissue may be built up even in the virgin to such an extent that at a certain stage fluid secretion occurs. This has been shown to be so by Woodman and Hammond[2] in the virgin heifer, in which mammary activity was found to take place during the œstrous cycle. In such animals they found in the udder the characteristic proteins (caseinogen, globulin, and albumen) of colostrum, together with small amounts of fat, lactose, and proteose.

The correlation between the generative organs and mammary glands in the guinea-pig has been dealt with in a series of papers by Leo Loeb.[1] He states that the presence of well-preserved corpora lutea does not lead to proliferation in the mammary tissue until a comparatively late stage of pregnancy (namely, after the twenty-fourth day). He remarks that the guinea-pig appears to differ from the rabbit in this respect, in that in the former animal the stimulus has to accumulate for a considerable period before reaction sets in. But in guinea-pigs castrated during pregnancy, and in which the pregnancy continued, proliferative changes were absent in the mammary gland. Complete extirpation of the corpora lutea similarly prevents the active secondary proliferation of the glands which occurs at a late stage.[2] The rat differs from the guinea-pig in that the corpus luteum persists for a considerable time during lactation, and perhaps consequently ovulation and heat are inhibited during the nursing period of the rat, while in the guinea-pig they continue to take place. The effects of castration on the lactating glands of the rat and guinea-pig are not noticeable until suckling ceases, when involution sets in. With regard to the nature of the stimulus calling forth lactation Loeb says it is neither purely functional nor purely formative but intermediate between the two.[3]

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[1] Biedl and Koenigstein, "Ueber das Mammahormon," *Zeitsch. f. Exp. Path. und Ther.*, vol. viii., 1910.

[2] Woodman and Hammond, "Note on the Composition of a Fluid obtained from the Udders of Virgin Heifers," *Jour. of Agric. Science*, vol. xii., 1922.

Steinach's experiments in which he transplanted ovaries into previously castrated guinea-pigs or rats are referred to elsewhere (see p. 346). He concludes that all the influence exercised by the ovary on the mammary glands is due to the interstitial or puberty gland, which promotes mammary growth and secretion. Athias[4] has described similar experiments on guinea-pigs, and, as a result of studying the histology of the transplanted ovaries, is of opinion that the development of the mammary glands and the initiation of milk secretion depend upon hypertrophied theca cells or ripe follicles. Both these investigators, therefore, contrary to the views of Ancel and Bouin and others, conclude that the presence of corpora lutea is unnecessary for the development of the mammary glands. It would seem possible that the guinea-pig may differ from the rabbit in this respect, or more probably that under certain conditions glandular elements in the ovary, other than corpora lutea, may take over the function of the latter organs. In this connection it may be recalled that according to Loeb the primary growth of the mammary glands takes place before ovulation, and the main or secondary growth is postponed until a later phase when the corpora lutea have been in existence for some time.

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[1] Loeb and Hesselberg, "The Cyclic Changes in the Mammary Gland, etc.," *Jour. Exp. Med.*, vol. xxv., 1917; Loeb and Kuramitsu, "The Influence of Lactation," "The Involution of the Uterus, etc.," and "The Effect of Suckling," *Amer. Jour. Physiol.*, vols. lv. and lvi., 1921; and Loeb, "The Relation of the Ovary to the Uterus and Mammary Gland," *Trans. Amer. Gyn. Soc.*, 1917.

[2] Extirpation of corpora lutea in the guinea-pig, according to this author, accelerates ovulation and heat and the associated primary proliferation of the mammary gland.

[3] A functional stimulus is one leading to activity unaccompanied by growth; a formative stimulus leads to a multiplication of cells and nuclei, *i.e.* to growth generally and to differentiation (Virchow). In the mammary gland secretion is accompanied by amitotic nuclear division. Mitotic proliferation precedes and follows secretion, but is not associated with actual secretion.

[4] Athias, "L'Activité Sécrétoire de la Glande Mammaire Hyperplasiée," *C. R. de la Soc. de Biol.*, vol. lxxviii., 1915; "Etude Histologique d'Ovaires Greffés," and "Sur le Déterminisme de l'Hyperplasie," *C. R. de la Soc. de Biol.*, vol. lxxix., 1916.

It has been shown that extract of corpus luteum has a marked galactogogue effect, intravenous injection resulting in an immediate outpouring of milk. This was first demonstrated by Ott and Scott[1] in the goat and has since been confirmed for man and other animals by Sharpey Schafer,[2] and Mackenzie,[3] and Gavin.[4] Ott and Scott were the first to show also that extract of posterior lobe of pituitary gland had an even more marked result. Extracts of placenta, involuting uterus, and pineal gland were similar, as well as the lactating gland itself. According to Hammond[5] the pituitary and other extracts probably act directly on the gland-cells, and it seems certain that more milk may be drawn off than could have been present in the sinuses and ducts at the moment of injection. The extract, therefore, must cause the glands to secrete. Sharpey Schafer,[6] however, is of opinion that the hormone acts on the unstriated muscle cells in much the same kind of way as extract of pituitary or corpus luteum causes contraction of the muscle of the uterus. Sharpey Schafer states further that the ovary appears to secrete two excitants, one increasing the contractility of muscle, the other inhibiting it.

Simpson and Hill,[7] however, differ from Sharpey Schafer and point out that barium chloride, which is a specific stimulus for muscle, has no effect on the milk flow.

It is probable, therefore, that the corpus luteum is normally an essential factor in both mammary growth and the initiation of mammary secretion, and no contradiction is involved in the assumption that the hormone or hormones when gradually secreted into the circulating blood in a state of nature act differently from the sudden injection of a considerable quantity of the substances. It is possible also that the hormone which has the power of increasing muscular contractility is produced in greater abundance at about the time of parturition (see p. 577).

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[1] Ott and Scott, "The Galactogogue Action of the Thymus and Corpus Luteum," *Proc. Soc. Exp. Biol. and Med.*, vol. viii., 1910. See also Ott's *Contributions to Physiology*, Part xix., 1912.

[2] Schafer and Mackenzie, "The Action of Animal Extracts on Milk Secretion," *Proc. Roy. Soc.*, B., vol. lxxxiv., 1911.

[3] Mackenzie (K.), "An Experimental Investigation of the Mechanism of Milk Secretion," *Quar. Jour. Exp. Physiol.*, vol. iv., 1911. Hill and Simpson, "The Effect of Pituitary Extract on Milk Secretion in the Goat," *Quar. Jour. Exp. Biol.*, vol. viii., 1914. See also *Amer. Jour. of Physiol.*, vol. xxxv., 1914, and *Proc. Soc. Exp. Biol. and Med.*, vol. xi., 1914.

[4] Gavin, "On the Effects of Administration of Extracts of Pituitary Body and Corpus Luteum to Milch Cows," *Quar. Jour. Exp. Physiol.*, vol. vi., 1913.

[5] Hammond, "The Effect of Pituitary Extract on the Secretion of Milk," *Quar. Jour. Exp. Physiol.*, vol. vi., 1913.

[6] Sharpey Schafer, *The Endocrine Organs*, London.

[7] Simpson (S.) and Hill, "The Mode of Action of Pituitary Extract," *Quar. Jour. Exp. Physiol.*, vol. viii., 1915. See also Schafer's Note to this paper.

It has been already shown that after ovariotomy lactation may be prolonged for an almost indefinite period, and further, that after the same operation the pituitary gland undergoes hypertrophy. It is not unlikely that these two facts are correlated, and that after the removal of the ovaries the function of the corpus luteum in relation to milk secretion may be taken over vicariously by the pituitary, which, unlike the luteal gland, does not atrophy after a comparatively short period. Such a conclusion, however, is at the best a very tentative one, for although the corpus luteum in *Dasyurus*[1] and the rat[2] is said to persist during lactation, it is not known how long the organ continues to function in other Mammals.[3] Relatively to the duration of suckling the corpus luteum in most species probably persists for only a short time.

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[1] Sandes, "The Corpus Luteum of *Dasyurus*," *Proc. Linn. Soc. N.S.W.*, vol. xxviii., 1903.

[2] Watson (B. P.), "On the State of the Ovaries during Lactation," *Proc. Phys. Soc.*, *Jour. of Physiol.*, vol. xxxiv., 1906.

[3] The part of the pituitary which hypertrophies after ovariotomy is said to be the anterior lobe, while the part that elaborates the galactogogue is the posterior lobe. The hypothesis suggested above, therefore, assumes a functional relation between the two lobes of which there is some evidence.

CHAPTER XIV

FERTILITY

> "Nam multum harmoniæ veneris differre videntur.
> Atque alias alii complent magis ex aliisque,
> Succipiunt aliæ pondus magis inque gravescunt.
> . . . .
> Atque in eo refert quo victu vita colatur."
>
> —LUCRETIUS.

THE rate of propagation in any species of animal depends not only upon the average number of young born in each litter, but also upon the frequency of recurrence of the sexual season and the duration of the reproductive period in the animal's life. The frequency of recurrence of the sexual season—that is to say, the œstrous cycle—in different species of Mammals has been discussed at some length in an early chapter of this work. In the present chapter it remains to consider a little more closely some of the causes which control this periodicity and the factors which affect fertility.

The duration of the reproductive period of an animal's existence extends in most cases from a time when that animal has almost reached its full size until the beginning of senescence, so that the normal period of generative activity in the individuals of any given species bears a definite relation to their average length of life. In the male the sexual maturity is usually reached later than in the female. Moreover, in the male there is no definite ending of the reproductive period, since in man, for example, the power of producing spermatozoa continues in a gradually diminishing degree even in extreme old age, whereas in the female, on the other hand, the climacteric marks the cessation of generative activity (see below, p. 714).

Broadly speaking, the average number of young produced in a litter in any species of Mammal is inversely proportional to the average size of the animals belonging to that species. Thus, in most species of Ungulates twins are the exception rather than the rule; and there are seldom more than two young produced at a time even in sheep and goats, which show a greater degree of fertility than most Ungulates. The sow, however, is exceptional in having very large litters, as many as seventeen young being sometimes born. On the other hand, in small Mammals such as Rodents large litters are the rule; the rat, for example, being known occasionally to bear as many as sixteen or even twenty young; but the Cheiroptera, or bats, are remarkable for their relative infertility, only one young one ordinarily being produced at a time, although the common bat is no larger than the mouse.

Generally speaking, only one young one is produced in those animals in which the period of gestation exceeds six months. The number of teats characteristic of the species also affords an approximate indication of the average size of the litter.

"Among women, the birth of twins occurs once in about eighty deliveries. Triplets, quadruplets, quintuplets, and even higher figures, are occasionally observed; they are very uncommon, and the rarity is progressive with the number. The normal or ordinary rule in woman is to bear one child at a time; and the next most frequent condition is temporary or persistent sterility—two points in which she signally differs from what is generally believed [of animals]."[1] Veit's statistics[2] for 13,000,000 births in Prussia showed that twins were produced once in 89 cases, triplets once in 7910, and quadruplets only once in 371,125 cases. There is some evidence also that the frequency of occurrence of multiple pregnancy in women depends upon the race or climate, and that it is commoner in cold than in warm countries.[3]

Herbert Spencer[4] elaborated a theory whereby he explained the relative degrees of fertility in the different races of men and animals. According to this theory the power to sustain individual life and the power to produce new individuals are inversely proportional, a conclusion which is summarised in the generalisation that Individuation and Genesis vary inversely. When there is an abundant food supply and a favourable environment, and the necessary expenditure of energy is relatively slight, the cost of Individuation is much reduced, and the rate of Genesis is correspondingly increased; in other words, there is a high degree of fertility. Spencer cited the Boers, the Kaffirs, and the French Canadians as examples of fertile races in which the rate of increase is associated with a nutrition that is greatly in excess of the expenditure. Conversely, he concluded that a relative increase of expenditure leaving a diminished surplus reduces the degree of fertility, and in support of this statement adduced evidence that bodily labour tends to make women less prolific, since the reproductive age is said to be reached a year later by women of the labouring class than by middle-class women.

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[1] Matthews Duncan, *Fecundity, Fertility, Sterility, and Allied Topics*, Edinburgh, 1866.

[2] Veit, "Beiträge zur geburtshülflichen Statistik," *Monatsschr. f. Geb.*, vol. vi., 1855.

[3] For further statistics and references see Williams, *Obstetrics*, New York, 1904.

[4] Spencer, *Principles of Biology*, Revised Edition, vol. ii., London, 1899.

Spencer applied his generalisation to animals as well as to man, and attempted to explain thereby the average contrast between the fertility of birds and Mammals. "Comparing the large with the large and the small with the small, we see that creatures which continually go through the muscular exertion of sustaining themselves in the air and propelling themselves rapidly through it, are less prolific than creatures of equal weights which go through the smaller exertion of moving about over solid surfaces. Predatory birds have fewer young ones than predatory Mammals of approximately the same sizes. If we compare rooks with rats, or finches with mice, we find like differences. And these differences are greater than at first appears. For whereas among Mammals a mother is able, unaided, to bear and suckle and rear half-way to maturity a brood that probably weighs more in proportion than does the brood of a bird; a bird, or at least a bird that flies much, is unable to do this. Both parents have to help; and this indicates that the margin for reproduction in each adult individual is smaller."

Spencer cites numerous instances from among both birds and Mammals illustrating the effects of different degrees of activity upon fertility. The hare and the rabbit, for example, are closely allied species, "similar in their diet, but unlike in their expenditures for locomotion. The relatively inert rabbit has six young ones in a litter, and four litters a year; while the relatively active hare has but two to five in a litter. That is not all. The rabbit begins to breed at six months old; but a year elapses before the hare begins to breed. These two factors compounded result in a difference of fertility far greater than can be ascribed to unlikeness of the two creatures in size."

Furthermore, Spencer refers to the case of the bat, which has been already mentioned as being abnormally unprolific in proportion to its size. The relatively low rate of multiplication is of course ascribed to a relatively high rate of expenditure resulting from the habit of flying.

In a similar way Spencer explains such well-known facts as that hens cease to lay when they begin to moult. "While they are expending so much in producing new clothing, they have nothing to expend for producing eggs."

There can be little doubt that Spencer's generalisation is in the main true, but it is equally certain that it cannot be applied indiscriminately to explain the relative degrees of fertility in all animals, and consequently it must not be pressed too far. Some of the more special factors which control fertility are referred to below, and it is evident that many (though not all) of these fall within the scope of Spencer's generalisation.

The rate of increase as distinguished from the rate of reproduction (in any given species) depends upon a large number of factors, of which the rate of reproduction is only one.

EFFECT OF AGE

Matthews Duncan[1] has discussed at some length the variation which occurs in the fertility of women according to their age. He adduces statistical evidence showing that the fertility of the female population increases gradually from the commencement of the child-bearing period of life until about the age of thirty, and then it gradually declines. He shows also that the fertility is much greater before the climax is reached (at thirty years) than after it is passed. These conclusions, however, apply merely to the actual productiveness (*i.e.* the number of births), as opposed to the capability of bearing children, which Duncan designates the fecundity. By eliminating from his calculations all women not living in married life, Duncan arrives at the following conclusions, which are based on statistics showing the productiveness of wives:[2] (1) "That the initial fecundity of women gradually waxes to a climax, and then gradually wanes"; (2) "That initial fecundity is very high from twenty to thirty-four years of age"; and (3) "That the climax of initial fecundity is probably about the age of twenty-five years." The fecundity of the average individual woman may be described, therefore, as forming a wave which, starting from sterility, rises somewhat rapidly to its highest point, and then gradually falls again to sterility.

Pearl[3] refers to the case of a ewe whose complete breeding record conforms to this description very closely. In her first two years she had single lambs, in her third year twins, then for six years in succession triplets, for the next six years twins, and finally for two more seasons single lambs. In the next two years which were the last of her life this ewe did not produce any lambs.

There can be no doubt that the majority of animals tend to follow a similar law. A dog generally has fewer puppies in its first litters than afterwards, while in its declining years there is a diminution until sterility is reached once more. The same is said to be the case with the bear, the elk, and other animals,[4] but there are obviously many individual exceptions. Minot[1] observed that in guinea-pigs the size of the litters increased with age during the first sixteen months of their lives; Hammond,[2] on the authority of the late Major P. G. Bailey, makes a similar statement for the rabbit; and Jones and Rouse,[3] who give a review of the literature, besides recording their own observations on various domestic animals, show that a similar general rule holds good for cattle, sheep, and pigs. Furthermore, King[4] found that rats reach the height of their reproductive capacity at about seven months, and that this age represents also the median point in the animal's breeding career.

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[1] Duncan, *loc. cit.*

[2] It is, of course, obvious that it is impossible to determine statistically the real "fecundity" (using the term as defined by Duncan) in view especially of the practice of volitional interference with conception (see below, p. 659).

[3] Pearl, "Note Regarding the Relation of Age to Fecundity," *Science*, vol. xxxvii., 1913.

[4] Duncan, *loc. cit.*

Geyelin[5] gives the following table showing the fertility of the domestic fowl at different ages:—

First year after hatching -	15 to 20
Second „ „ -	100 „ 120
Third „ „ -	120 „ 135
Fourth „ „ -	100 „ 115
Fifth „ „ -	60 „ 80
Sixth year after hatching -	50 to 60
Seventh „ „ -	35 „ 40
Eighth „ „ -	15 „ 20
Ninth „ „ -	1 „ 10

Pearl,[6] however, states that the greatest egg production is in the first year. With Barred Plymouth Rocks he found that reproductive ability diminished with advancing age, being at its maximum at ten to fourteen months. Robinson,[7] writing of fowls and ducks, says that few birds are as good breeders the third year as the second, and fewer still are good after the third year. "It is largely a question of condition; the older a bird grows, the more difficult it is to keep in good breeding condition."

EFFECTS OF ENVIRONMENT AND NUTRITION

That the generative system in animals is peculiarly susceptible to changed conditions of existence has been recognised from early days. Thus Aristotle[8] commented on the increased fertility of sheep in a favourable environment. In more recent times Buffon,[9] among others, remarked on the fact that domestic animals breed oftener and produce larger litters of young than wild animals belonging to the same species; and Darwin, who made the same observation, attributed the increased fertility of the former to a long habituation to a regular and copious food supply without the labour of seeking for it. "It is notorious how frequently cats and dogs breed, and how many young they produce at birth. The wild rabbit is said to breed four times yearly, and to produce each time at most six young; the tame rabbit breeds six or seven times yearly, producing each time from four to eleven young. . . . The ferret, though so closely confined, is more prolific than its supposed wild prototype [the polecat]. The wild sow is remarkably prolific; she often breeds twice in the year, and bears from four to eight, and sometimes even twelve, young; but the domestic sow regularly breeds twice a year, and would breed oftener if permitted; and a sow that produces less than eight at birth 'is worth little, and the sooner she is fattened for the butcher the better.' The amount of food affects the fertility of the same individual; thus sheep which on mountains never produce more than one lamb at birth, when brought down to lowland pastures frequently bear twins. The difference apparently is not due to the cold of the higher land, for sheep and other domestic animals are said to be extremely prolific in Lapland."[1]

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[1] Minot, "Senescence and Rejuvenation," *Amer. Jour. of Physiol.*, vol. xii., 1891.

[2] Hammond, "On some Factors controlling Fertility in Domestic Animals," *Jour. of Agric. Science*, vol. vi., 1914.

[3] Jones and Rouse, "The Relation of Age of Dam to observed Fecundity," *Jour. of Dairy Science*, vol. iii., 1920. See also article by Harrison, *Amer. Naturalist*, vol. l., 1916.

[4] King, "The Relation of Age to Fertility in the Rat," *Anat. Record*, vol. xi., 1916.

[5] Geyelin, *Poultry-Breeding in a Commercial Point of View*, London, 1865.

[6] Pearl, "The Mode of Inheritance of Fecundity in the Domestic Fowl," *Jour. Exp. Zool.*, vol. xiii., 1912; "Studies in the Physiology of Reproduction in the Domestic Fowl," XVII., *Genetics*, vol. ii., 1917.

[7] Robinson (J. H.), *Principles and Practice of Poultry Culture*, Boston, 1912.

[8] Aristotle, *History of Animals*, Bohn's Library, London.

[9] Buffon, *Histoire Naturelle*, Paris, 1802.

Darwin remarks that birds afford still better evidence of increased fertility resulting from domestication. Thus, in its natural state the female of *Gallus bankiva*, the wild representative of the common fowl, lays only from six to ten eggs; the wild duck lays from five to ten eggs, as compared with eighty or a hundred produced by the domestic duck in the course of the year. Similarly, the turkey, the goose, and the pigeon are more fertile in the domestic state, though this is not the case with the pea-fowl. Among plants also there are countless instances of increased fertility as a consequence of cultivation.[2]

On the other hand, it is well known that wild animals, when removed from their natural conditions and brought into captivity, often become partly or completely sterile. Darwin discusses this phenomenon at some length, and cites numerous cases from different groups of animals and birds.

The Indian elephant, for example, seldom breeds in captivity, although kept in a perfectly healthy condition and in its native country. On the other hand, most members of the Suidæ are known to breed in menageries and zoological gardens, while many

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[1] Darwin, *The Variation of Animals and Plants under Domestication*, Popular Edition, vol. ii., London, 1905.

[2] *Cf.* also Spencer (*loc. cit.*), who discusses this question at some length in connection with his generalisation that Individuation and Genesis vary inversely. See above, p. 624.

Ruminants breed readily in climates widely different from their own. Carnivorous animals breed somewhat less freely in confinement, and show considerable variation in different places. The Canidæ tend to be more fertile than the Felidæ, while the members of the bear group breed less easily. Rodents as a general rule fail to breed after being brought into captivity, but there are several exceptions. Monkeys also when kept in confinement only rarely have young ones. Many of these animals, however, although failing to conceive, are known to copulate freely. This is especially the case with captive bears and monkeys, in which the typical phenomena of proœstrum and œstrus occur. It would seem probable that the sterility under these circumstances results from a failure to ovulate, due possibly to an absence of ripe follicles in the ovaries.

Among birds, members of the hawk group very seldom breed in captivity. The graminivorous birds show considerable variation, some, like the canary, breeding freely in aviaries (although it was some time before it became fully fertile), while others, like the finches, only occasionally reproduce their kind when kept in confinement. Gallinaceous birds, on the other hand, show an unusual capacity to breed in captivity, and the same is the case with pigeons, ducks, and geese. Certain kinds of gulls also are known to breed readily when kept in open spaces in zoological gardens.

As pointed out by Darwin, there is other evidence that changed conditions of life may induce a disturbance of the sexual functions. Thus when conception does occur under confinement, the offspring are sometimes born dead or ill-formed, or otherwise show signs of insufficiency of nourishment. The mother's milk may fail, indicating an interference with those factors which control the mammary metabolism. Moreover, in animals which are characterised by a periodic growth of the secondary sexual characters, these sometimes fail to make their appearance. The male linnet in captivity does not assume its characteristic crimson breast, or the male bunting (*Emberiza passerina*) the black colour on its head. Other birds, such as a pyrrhula and an oriole, may acquire the appearance of the hen, while a falcon (*Falco albidus*) has been observed to lose its adult plumage.[1] These facts seem to show that the generative metabolism may be so altered by changed conditions of existence as to induce not merely a state of sterility, but also an interference with the secretory activity of the essential organs of reproduction.[2]

Darwin says: "We feel at first naturally inclined to attribute [such results] to loss of health, or at least to loss of vigour; but this view can hardly be admitted when we reflect how healthy, long-lived, and vigorous many animals are under captivity, such as parrots, and hawks when used for hawking, chetahs when used for hunting, and elephants. The reproductive organs themselves are not diseased;[1] and the diseases from which animals in menageries usually perish are not those which in any way affect their fertility. The failure of animals to breed under confinement has been sometimes attributed exclusively to a failure in their sexual instincts. This may occasionally come into play, but there is no obvious reason why this instinct should be especially liable to be affected with perfectly tamed animals, except, indeed, indirectly through the reproductive system itself being disturbed. Moreover, numerous cases have been given of animals which couple freely under confinement, but never conceive; or, if they conceive and produce young, these are fewer in number than is natural to the species. . . . Change of climate cannot be the cause of the loss of fertility, for whilst many animals imported into Europe from extremely different climates breed freely, many others when confined in their native land are sterile. Change of food cannot be the chief cause; for ostriches, ducks, and many other animals, which must have undergone a great change in this respect, breed freely. Carnivorous birds when confined are extremely sterile, whilst most carnivorous Mammals, except plantigrades, are moderately fertile. Nor can the amount of food be the cause; for a sufficient supply will certainly be given to valuable animals; and there is no reason to suppose that much more food would be given to them than to our choice domestic productions which retain their full fertility. Lastly, we may infer from the case of the elephant, chetah, various hawks, and of many animals which are allowed to lead an almost free life in their native land, that want of exercise is not the sole cause." Darwin shows also that close confinement by itself does not necessarily cause sterility, since such animals as the rabbit and ferret breed freely in cramped hutches. The general conclusion reached is that "any change in the habits of life, whatever these habits may be, if great enough, tends to affect in an inexplicable manner the powers of reproduction. The result depends more on the constitution of the species than on the nature of the change; for certain whole groups are affected more than others; but exceptions always occur, for some species in the most fertile groups refuse to breed, and some in the most sterile groups breed freely."

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[1] Darwin, *loc. cit.*

[2] The relation between the gonads and the secondary sexual characters, and the apparent dependence of the latter upon the secretory activity of the former, are discussed in Chapter IX.

In support of these conclusions Darwin shows further that domesticated animals also under new conditions occasionally show signs of lessened fertility, and that animals such as the canary, which now breed readily in a state of captivity, were formerly often sterile.

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[1] Few observations have been made upon the condition of the gonads in animals in captivity, but Branca ("Recherches sur le Testicule et les Voies spermatiques dans Lémuriens en captivité," *Jour. de l'Anat. et la Phys.*, vol. xl., 1904) states that in captive lemurs he could find no spermatozoa in the testicles.

Bles's observations,[1] to which reference has already been made (p. 18), seem to have a bearing on this question. This observer, who has kept various kinds of Amphibia in captivity, has shown that axolotls can only be induced to breed under certain special environmental conditions. By feeding them copiously in summer and allowing them to hibernate in winter, and then suddenly transferring them to an aquarium stocked with growing plants and provided with running water, these animals could be induced to spawn within a few days. (*Cf.* also Annandale's observations referred to on p. 20.) Bles draws the conclusion that the difficulty so often experienced in inducing Amphibians to breed in a state of captivity is not due to toxic influence on the gonads resulting from the confinement, but must rather be ascribed to the absence of the necessary external stimuli without which the generative organs of animals are incapable of properly discharging their functions. Bles suggests that this view may help to explain why some animals (*e.g.* insects) make their appearance in great numbers in one year, and are comparatively scarce in another.

In animals which as a general rule breed freely in a state of domestication or under confinement, it is probable that nutrition plays the chief part (though by no means the sole part) in regulating the capacity to produce offspring. That an insufficient or markedly abnormal diet must affect this power is almost self-evident, and Chalmers Watson[2] has shown that sterility is a common condition among caged rats when fed exclusively upon meat.[3] It is also certain that an excessive quantity of nutriment is likewise prejudicial to the proper discharge of the reproductive functions. No better example could be given of the way in which overfeeding results in a condition of sterility than that of the barren Shire mares, which in some past years have been a striking feature at agricultural shows in England. Some foods are said to induce sterility more easily than others. Sugar, molasses, and linseed are noted for having this effect when given to cattle, but they are often used to prepare beasts for show or sale, since they produce a good coat of hair and cause a deposit of fat. Very fat animals do not come in season so often, and consequently cattle "settle better and feed faster as they become what the butchers designate 'fat ripe.'" In such animals there can be no doubt that the ovarian metabolism is abnormal, and the author has often found large quantities of bright orange-coloured lipochrome in the interstitial tissue of the ovaries of fat cows and heifers.[1] Kirkham [2] records sterility in white and yellow mice which after four to six litters lay down extensive quantities of fat and thenceforward fail to breed. In man also obesity is known to be a cause of sterility, in the male spermatogenesis being partly inhibited.[3]

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[1] Bles, "The Life-History of *Xenopus lævis*," *Trans. Roy. Soc. Edin.*, vol. xli., 1906.

[2] Campbell and Watson, "The Minute Structure of the Uterus of the Rat, etc.," *Proc. Phys. Soc.*, *Jour. of Physiol.*, vol. xxxiv., 1906.

[3] *Cf.* Pezard on "alimentary castration" as a result of a meat diet in fowls (see above, p. 334). Moreover, Allen has shown that a deficiency of water-soluble vitamins in the diet given to rats causes atrophy of the seminiferous tubules of the testis (*Anat. Record*, vol. xvi., 1919).

A low condition, especially if associated with exposure to wet and cold, as in the case of cattle wintered in the open air, or of cows which have suckled a large calf or more than one calf, is also a common cause of temporary barrenness.[4] Certain other more special causes of sterility are referred to briefly below (p. 644).

A few years ago the Royal Agricultural Society of England instituted an inquiry into the subject of fertility in sheep. The investigation was conducted by Heape, at whose instigation it was carried out. In the report,[5] which was subsequently published a comparative account is given of the fertility of various breeds of sheep chiefly in the South of England in the season 1899. The most fertile breed was the Wensleydale, in which six flocks, consisting of a total of 319 ewes, produced a percentage of 177·43 lambs. The effects of locality are discussed, and there is an accumulation of evidence indicating that the character of the district is not without influence on the fertility of the breed. Thus, Lincoln sheep run on the wolds, Shropshire sheep on a subsoil of New Red Sandstone, and Hampshire sheep, which are not run upon chalk downs, are shown to be associated statistically with a relatively high percentage of infertility. The report shows further that the fertility of a flock depends greatly upon its management, that the quality and quantity of the food supplied affect the condition of the sheep, and so influence their power to breed, that some seasons are more favourable to fertility than others, and that sheep-stained pasture (or pasture on which sheep have run for some considerable time previously) is detrimental to breeding stock.

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[1] Marshall and Peel, "Fatness as a Cause of Sterility," *Jour. of Agric. Science*, vol. iii., 1910. The lipochrome may have belonged to persistent corpora lutea.

[2] Kirkham, "The Life of the White Mouse," *Proc. Soc. Exp. Biol. and Med.*, vol. xvii., 1920.

[3] Cooper, *The Sexual Disabilities of Man*, London, 1918.

[4] Wallace (R.), *Farm Live Stock of Great Britain*, 4th Edition, Edinburgh, 1907.

[5] Heape, "Abortion, Barrenness, and Fertility in Sheep," *Jour. Roy. Agric. Soc.*, vol. x., 1899. See also Heape, "Note on the Fertility of Different Breeds of Sheep, etc.," *Proc. Roy. Soc.*, vol. lxiv., 1899.

The present writer has shown[1] that in Scotch Blackfaced, Cheviot, and other Scottish sheep the normal percentage of ova discharged at any single œstrous period is not appreciably in excess of the usual percentage of births at the lambing season. It would seem probable, therefore, that a scarcity of twin births at lambing time is the direct consequence of an abnormally low number of ripe follicles in the ovary at tupping time (*i.e.* during the sexual season). A low percentage of twins is generally associated with barrenness, a fact which is recognised by flockmasters, and which is proved very clearly by Heape's statistics. And since ewes which are constitutionally barren are a rarity, there can be little doubt that infertility among sheep is due ordinarily to an absence or great scarcity of follicles available for ovulation at tupping time.

Scarcity of mature follicles must itself result either from a retardation in follicular development or from an unusual tendency towards follicular degeneration whether occurring shortly before the sexual season or at some previous period in the animal's lifetime. Atretic or degenerate follicles are by no means uncommon in sheeps' ovaries, the process of atresia appearing to set in most commonly in follicles which have reached a size varying from about one-eighth to one-half the dimensions of the mature follicle. It may set in, however, at practically any stage of development and probably in the so-called primordial follicle (see p. 151). There can be little doubt that an excessive follicular degeneration results usually from an insufficiency of stimulating power at the disposal of the ewe.

That a relative scarcity of ripe follicles in sheeps' ovaries at the sexual season is due to retardation of development is a conclusion which is based on inference rather than observation, for little is known regarding the actual rate of growth of the Graafian follicle. Nevertheless, there is every reason for supposing that the processes of growth and maturation can be very largely influenced both by insufficiency of food supply on the one hand and by artificial stimulation on the other, as has been shown for other animals. This fact has been recognised for years past by certain individual flockmasters who have consistently practised the methods of "flushing" or artificially stimulating their ewes by means of an extra supply of special food at the approach of the tupping season, but no precise records of the effects of this process had been published until lately, when the Highland and Agricultural Society of Scotland undertook an investigation upon this subject.

In the report which has since been issued,[2] and which contains the lambing statistics for various flocks of Scottish sheep for the years 1905, 1906, and 1907, it is shown that the percentage of lambs born was, as a general rule, highest among sheep which had been subjected to a process of artificial stimulation. The method adopted was to feed the ewes upon turnips, oats, maize, dried grains, or other additional food at the tupping time and for about three weeks previously, while maintaining them upon grass only during the greater part of the year. Some flocks, however, received a limited supply of extra food (generally turnips) during gestation, and especially during the later part of this period. The additional supply of turnips, which are specially rich in carbohydrate material, was found to be in no way detrimental to fertility, but rather the reverse, when accompanied by other food (pasture), and so not taken in excess. The statistics show that in the flocks treated in the way described, the percentage of lambs per ewes[1] was almost invariably in excess of the average percentage for flocks which received no special treatment, while the percentage of barren ewes was usually also less in the specially fed flocks. In some cases the number of lambs per ewes in the flushed flocks was nearly 200 per cent. Among flocks belonging to the same breeds (Border Leicester or half-bred Border Leicester) which received no sort of special treatment, the average proportion of lambs per ewes was between 150 and 160 per cent., while flocks which were run upon superior pasture at the approach of the sexual season, without being otherwise specially fed, generally produced a slightly larger percentage of lambs. The twins appear almost invariably to have been born early during lambing, thus showing that the generative activity of the ewes tends to be greatest at the commencement of the sexual season.

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[1] Marshall, "The Œstrous Cycle and the Formation of the Corpus Luteum in the Sheep," *Phil. Trans.*, B., vol. cxcvi., 1903.

[2] Marshall, "Fertility in Scottish Sheep," *Trans. Highland and Agric. Soc.*, vol. xx., 1908. See also *Proc. Roy. Soc.*, B., vol. lxxvii., 1905.

It has proved more difficult to obtain definite information concerning the effects of flushing in one year upon the fertility of the ewes in subsequent seasons. The more usual experience of flockmasters seems to be that flushing is not in any way prejudicial to breeding stock unless it is overdone, the object of the process being to get the animals in an improving condition without permitting them to put on too much fat. If the artificial feeding is excessive and the sheep are forced to depend for the remainder of the year upon a mere sustenance diet, it is easy to understand that they would tend to deteriorate, and their subsequent fertility become impaired, owing probably to a higher frequency of follicular degeneration. It is seemingly for such a reason that some flockmasters regard the practice of flushing as one altogether to be deprecated. There is some evidence, however, that if sheep are specially fed in one season, the process must be repeated in the next, and that if this is omitted the sheep tend to be less fertile than if they had never been subjected to flushing.

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[1] That is to say, the number of lambs per 100 ewes.

It has already been mentioned (p. 364) that the practice of flushing tends to hasten the sexual season, the sheep coming "on heat" sooner than they would otherwise. The result must be ascribed to a general increase in the ovarian metabolism consequent upon the stimulating power of the special food supply. Conversely, it has been shown that in ewes which are poorly fed the sexual season is often retarded, and the fertility of the flock reduced. So also the occurrence of a snowstorm, or other unfavourable climatic condition, occurring during tupping time will cause a corresponding scarcity of twin births in the following lambing season. There can be little doubt, therefore, that the conditions which exist during tupping time are largely responsible for controlling the fertility of the flock, and that favourable conditions tend to promote the more rapid growth and maturation of the follicles in the ovary, and cause a greater number to discharge their ova during the œstrous periods.

It would appear also that in ordinary agricultural practice the condition of the ewe is a far more important factor in determining the number of twin births than that of the ram; but it is obvious that the number of ewes which one ram can serve successfully must depend upon the degree of vigour possessed by him, and that the keeping of a ram which is partially sterile and yet is turned out to serve ewes must result in a reduction in the number of lambs (see below, p. 637).

The effects of nutrition upon the production of ripe follicles in guinea-pigs have been studied by Leo Loeb[1] who states that underfeeding if very pronounced prevents maturation in all cases, and causes atrophy before the follicles have reached medium size. A premature solution of the epithelial cells is brought about in this way, but the connective tissue of the ovary is more resistant to the effects of underfeeding. The cells which are furthest from the blood-vessels suffer first. The epithelial cells, however, continue to multiply as long as they survive, and this is ascribed to a normal growth stimulus which emanates from the ovum. The result of poverty of nutrition is more marked in the ovaries of young animals just as the general effect is greater, but a "hypotypical" condition can be induced even in old guinea-pigs. In an extreme case of hypotypical ovaries the connective tissue separating the follicles had become affected, being undeveloped or lacking, so as to result in a union of follicles and a consequent polyovular condition.[2] Loeb says that the hypotypical ovarian state leads to at least temporary sterility.

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[1] Loeb, "The Experimental Production of Hypotypical Ovaries through Underfeeding," *Biol. Bull.*, vol. xxxii., 1917.

[2] See footnote, p. 121.

Follicular atrophy is, however, a normal process probably in all the higher animals (see p. 153), and it is only when it becomes excessive that it is a cause of sterility, since the number of young ova and follicles is far larger than that of the young which could develop. Thus the human ovary is said to contain 20,000 oöcytes at puberty, or sufficient to admit of forty ova being discharged every month throughout the reproductive period of life. In the rat there are, according to Arai,[1] 35,100 ova at birth, but these are reduced by degeneration to 11,000 after twenty-three days and 6000 by the sixty-third day. Moreover, according to Robinson,[2] in the ferret the smaller follicles are necessary for providing nourishment for the larger developing ones.

Moreover, Hammond[3] has shown that in the domestic animals, and especially in the pig and tame rabbit, fecundity is apt to be conditioned rather by the factors controlling development *in utero* than by the production of ova. The number of eggs matured is frequently in excess of the nutrition available for them, and this leads them to atrophy, sometimes while still contained in the ovarian follicles, but also very frequently as newly fertilised ova or partially developed embryos.

The effect of external conditions on the rate of follicular ripening in the rabbit has also been studied by Hammond, who states that in the wild state the number of eggs discharged increases from January to April and then decreases. This is similar to what occurs in the domestic fowl. With tame rabbits the effect is not so marked owing to the more uniform conditions under which they are kept. The average number of eggs shed at one period was found to be 5·74 in wild rabbits and 10·3 in domesticated rabbits, but in the latter atrophic fœtuses are much more common (see below, p. 656).

INFLUENCE OF THE MALE PARENT

It has been suggested that in some males there is a want of vigour on the part of the spermatozoa which either prevents them from conjugating with ova or causes abortion of the fertilised ovum or fœtus owing to its being endowed with a reduced vitality. Stephenson[4] refers to cases of bulls which had at one time been

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[1] Arai, "On the Post-Natal Development of the Ovary, etc.," *Amer. Jour. of Anat.*, vol. xxvii., 1920.

[2] Robinson (A.), "The Formation, etc., of the Graafian Follicle in the Ferret, etc.," *Trans. Roy. Soc. Edin.*, vol. lii., 1918.

[3] Hammond, "Further Observations on the Factors controlling Fertility and Fœtal Atrophy," *Jour. Agric. Science*, vol. xi., 1921.

[4] Stephenson, "Abortion in Cows," *Jour. Roy. Agric. Soc.* vol. xxi. (2nd series), 1885.

"good getters" but were afterwards responsible for cows being sterile or aborting at different stages of pregnancy, and he explains them in this way. Hammond[1] describes what he suggests may have been another such case of a bull, for he found that the semen of the animal in question only contained occasional spermatozoa which, in contrast to those obtained from other bulls, showed no sign of movement. There can, however, be little doubt that ordinarily spermatozoa in amply sufficient numbers are ejaculated at one service to fertilise all the ova discharged by the female. Moreover, Hammond found that with the male rabbit after repeated coition (even up to the thirty-seventh time and within eight hours) there was no reduction in the fertility of the females which were served. The delay periods, however, between the later copulations were slightly increased. Contrary to Hammond's results Lloyd-Jones and Hays[2] had previously found that excessive copulation by the male rabbit produced a reduction both in the number of pregnancies and in the size of the litters.

It is said that a good stallion should be able to serve eighty mares in one season, but Hammond has pointed out that there may be no reduction in the fertility of the mares even though as many as 140 are served. At the same time, the records of one province have shown that the percentage of foals left by different stallions can vary from twenty-seven to seventy-five.[3] The usual proportion of ewes put to one ram is about fifty, but ram lambs are not permitted to serve more than about twenty ewes. Similarly with stallions, when they are two years old they are not allowed to have intercourse with more than sixty mares as compared with 80 to 120 for adult stallions. It is not suggested, however, that if a larger number of services were permitted the unions would be sterile, but that too frequent intercourse has a deteriorating influence on the vigour of the male. Even yearling stallions are sexually mature but are never allowed more than fifteen mares, and generally none at all.

EFFECT OF PROLONGED LACTATION

It has been recorded that the continuance of lactation commonly exerts an inhibitory influence on menstruation in women and on heat in animals, though this is very far from being invariable (see p. 69). There can be no doubt that in the case of sows, for example, early weaning is conducive to a more frequent recurrence of œstrus and an increased number of litters (see p. 46). In a similar way long-continued lactation is believed to reduce the fecundity of women, who sometimes refrain from weaning their babies in the belief that by so doing they are less liable to become pregnant again. Moreover, Haddon's observations[1] upon the Eastern Islanders of the Torres Straits show that with these people also prolonged nursing tends to reduce the size of the families, and that a single lactation may be continued for three years

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[1] Hammond, *loc. cit.*

[2] Lloyd-Jones and Hays, "Influence of Excessive Sexual Activity in Male Rabbits," *Jour. Exp. Zool.*, vol. xxv., 1918.

[3] Marshall and Crosland, "Sterility in Mares, etc.," *Jour. Board of Agric.*, vol. xxiv., 1918.

EFFECT OF DRUGS

There is little evidence as to the effects of drugs upon egg- or sperm-production, but innumerable substances have been recommended as cures for impotence.[2] Cantharides and various other drugs are said to produce sexual excitement, but this result is probably due simply to the increased flow of blood to the generative organs which these substances induce.[3] Wallace says that the practice adopted by some grooms of giving cantharides to stallions is strongly to be deprecated. Bloch is disposed to recommend the use of phosphorus and strychnine in the treatment of impotence in men, but the most favourable results have been obtained by yohimbine, an alkaloid prepared from the bark of a West African tree. Bloch mentions several cases where, in his own experience, treatment by yohimbine has been entirely successful, and there are numerous others on record. Many veterinarians also have testified to the powerful aphrodisiac action of yohimbine, stating further that it is capable of inducing a condition of heat in domestic animals and acting as an effective remedy for certain kinds of sterility.

Daels[4] found that yohimbine when administered to dogs produced hyperæmia of the generative organs, followed by mucous and sanguineous discharge, but not true heat. Dr. Cramer and the present writer[5] have made similar observations. We first administered 0·005 gram of yohimbine twice daily for nearly a fortnight to each of two anœstrous bitches, the drug been swallowed in the form of tablets. Marked congestion of the generative organs followed. On treating rabbits with yohimbine the vulva and the uterine mucosa became excessively hyperæmic, the entire generative tract being affected to some extent. The ovaries were much overgrown by luteal tissue, and degenerate follicles which are generally so common in rabbits' ovaries were relatively scarce. Hammond,[1] however, failed to get any positive results on the fertility of rabbits after treatment with yohimbine. We obtained some evidence that yohimbine may promote mammary development and the secretion of milk.

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[1] Haddon, *Reports of the Cambridge Anthropological Expedition to Torres Straits*, vol. vi., Cambridge, 1908.

[2] For the distinction between sterility and impotence see below (p. 644). For detrimental results of drug action or abnormal treatment on sperm- or egg-production see also below (p. 647).

[3] Bloch, *The Sexual Life of our Time*, English Translation, London, 1908.

[4] Daels, "On the Relation between the Ovaries and the Uterus," *Surgery, Gynæcology and Obstetrics*, vol. vi., (February) 1908.

[5] Cramer and Marshall, "Preliminary Note on the Action of Yohimbine on the Generative System," *Jour. Econ. Biol.*, vol. iii., 1908.

Effects of In-Breeding and Cross-Breeding

The fact that in-breeding may result in a reduced fertility has been already discussed in dealing with the significance of the fertilisation process (pp. 215-220).[2] It was then pointed out that a tendency towards sterility may be associated with a constitutional loss of vigour. In the same place it was mentioned further that cross fertilisation between organisms which are allied but belong to different strains often results in an increased fertility, but that cross fertilisation between different species is frequently difficult to accomplish while there is every gradation between a mere disinclination towards gametic union and complete cross sterility.

The differences in fertility between varieties and species when crossed are discussed at some length by Darwin,[3] who summarises his general conclusions under seven heads. First, the laws governing hybridisation in plants and animals are practically identical. Secondly, there are all degrees of cross infertility. "Thirdly, the degree of sterility of a first cross between two species does not always run strictly parallel with that of their hybrid offspring. Many cases are known of species which can be crossed with ease, but yield hybrids excessively sterile; and conversely some which can be crossed with great difficulty, but produce fairly fertile hybrids. This is an inexplicable fact on the view that species have been specially endowed with mutual sterility in order to keep them distinct." Fourthly, the degree of sterility is often different in the two sorts of reciprocal crosses between the same species, and hybrids produced from reciprocal crosses sometimes differ in their degree of sterility. "Fifthly, the degree of sterility of first crosses and of hybrids runs, to a certain extent, parallel with the general or systematic affinity of the forms which are united.

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[1] Hammond, *loc. cit.*, 1921.

[2] A method of measuring the degree of in-breeding practised in any particular case has been devised by Pearl. It is based on the simple and definite conception that an in-bred animal has fewer different ancestors than one which is not in-bred, and coefficients of in-breeding have been constructed. For details of the method see *Maine Agric. Exp. Station Bulletins*, 215 and 243, Orono, 1913 and 1915.

[3] Darwin, *loc. cit.* See also *Origin of Species*, 6th Edition, London, 1872.

For species belonging to distinct genera can rarely, and those belonging to distinct families can never, be crossed. The parallelism is, however, far from complete; for a multitude of closely allied species will not unite, or unite with extreme difficulty, whilst other species, widely different from one another, can be crossed with perfect facility. Nor does the difficulty depend on ordinary constitutional differences, for annual and perennial plants, deciduous and evergreen trees, plants flowering at different seasons, inhabiting different stations, and naturally living under the most opposite climates, can often be crossed with ease. The difficulty or facility depends exclusively on the sexual constitution of the species which are crossed; or on their elective affinity." Sixthly, cross sterility between species may depend possibly in certain cases upon distinct causes, such as deterioration due to unnatural conditions to which the hybrid embryo may be exposed in the uterus, egg, or seed of the mother. "Seventhly, hybrids and mongrels present, with the one great exception of fertility, the most striking accordance in all other respects; namely, in the laws of their resemblance to their two parents, in their tendency to reversion, in their variability, and in being absorbed through repeated crosses by either parent form." It is obvious, however, that this last conclusion requires some modification in the light of recent Mendelian research.

Darwin maintains further that the cross fertility which exists between the different varieties of various species of domesticated animals, in spite of their great divergence in external appearance, is the direct effect of domestication which eliminates the tendency towards mutual sterility. In this way "the domesticated descendants of species, which in their natural state would have been in some degree sterile when crossed, become perfectly fertile together." Both Darwin and Wallace lay stress upon the apparent existence of a parallelism between crossing and change of conditions in so far as these affect the power to reproduce. "Slight changes of conditions and a slight amount of crossing are beneficial; while extreme changes, and crosses between individuals too far removed in structure or constitution, are injurious."[1] Furthermore, domestic animals are less susceptible to the influences of changed conditions of existence than wild animals, a fact which finds a parallel in the absence of sterility between domesticated varieties of the same species.

It is now clear that Darwin's views on in-breeding and on the results of that process must be modified in the light of recent Mendelian investigation, for, as already shown in an earlier chapter of this book, there is a growing body of evidence to show that different degrees of productivity down to complete sterility can be inherited as though they were Mendelian units. In the light of this conception the effects both of in-breeding and of cross-breeding would seem to acquire a new signification. It has been established that in some insects (*Drosophila*) complete sterility may be a sex-linked character, and the same is apparently true of the male tortoiseshell cat. It is suggested that in the famous Duchess family of Shorthorn cattle bred by Bates and which eventually became extinct, there was a factor for sterility present, and this as a result of close in-breeding kept on reappearing with increased frequency until no more fertile individuals were produced. It has been shown that with *Drosophila*, and also with the guinea-pig, a high degree of fertility can be maintained in successive generations of in-breeding by selecting from the more fertile individuals. Further, there is direct cytological evidence that in *Drosophila* sterility is correlated with the absence of a particular chromosome.[1]

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[1] Wallace (A. R.), *Darwinism*, London, 1897.

And conversely the increased vigour and fertility apparently brought about by cross-breeding and heterozygosis may be "due to the establishment of a more excellent factor-complex rather than to any mysterious stimulation effect of the heterozygous condition."[2] At the same time it is possible that the reproductive cells even in their hereditary composition are capable of being affected by their environment, and it is reasonable to suppose that in the unicellular organisms at any rate new and more favourable surroundings, acting in conjunction with an appropriate factor-complex, may have a stimulating and favourable influence on fertility.

The sterility of hybrids is a very common phenomenon and has received a cytological interpretation. Such infertility is, however, by no means invariable.

Wallace has cited several cases in which it has been shown that hybrids between distinct species are fertile *inter se*. Such cases are the hybrids between the domestic and Chinese geese, and the various hybrids between the different species of the genus *Canis*. A case of a fertile hybrid between a lion and a jaguar has been recorded also. The various members of the family Bovidæ are known to hybridise and to produce fertile offspring even though the parents belong to what are ordinarily regarded as different genera. The cow (*Bos taurus*) gives fertile male and female hybrids when crossed with the zebu (*Bos indicus*). With the yak (*Bibos grunnicus*), the gaur (*Bibos gaurus*), the gayal (*Bibos frontalis*) and the bison (*Bison americanus*) the cow has fertile female hybrids but sterile males.[3] The hybrids between the cow and *Bison bonasus* are similar.[1] These and other observations show that sterility among hybrids between closely allied species, although usual, is very far from being universal.[2] Similar cases have been recorded from among plants.

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[1] For an admirable discussion of the subject see Babcock and Clausen, *Genetics in Relation to Agriculture*, New York, 1918. This work contains many references. See also Morgan, *Heredity and Sex*, New York, 1913.

[2] Babcock and Clausen, *loc. cit.*

[3] Babcock and Clausen, *loc. cit.*

The cause of sterility in hybrid organisms is still to a large extent an open question. In some cases the generative organs are atrophied or imperfectly developed, while in most, if not all sterile hybrids, the gametes are not developed. For example, Iwanoff[3] states that hybrids between the horse and the zebra do not possess spermatozoa, though able to perform the sexual act.

It has been suggested that the sterility is due to irregularities in the mechanics of division in the germ-cells. "When we recall that at one stage in the development of the germ-cells there may be a pairing and subsequent fusion of the maternal and paternal chromosomes, we can readily imagine that any differences in their behaviour at this time might lead to disastrous results."[4]

It has been shown that irregular reduction divisions occur in the male, and that in hybrid pheasants a degeneration of germ-cells begins in synapsis. In some hybrids the number of chromosomes derived from each parent is different, but as Babcock and Clausen point out, the difficulty must be fundamentally physiological, since it is just as pronounced in hybrids between species having the same number of chromosomes.

Inheritance of Fertility

That fertility is a racial characteristic, and consequently is capable of hereditary transmission, is a fact that is generally accepted. Among sheep, for example, some breeds, like the Dorset Horns, the Hampshire Downs, and the Limestones, are notoriously prolific, while other varieties, like the Scotch Blackfaced, are relatively infertile.[5] Furthermore, there is a considerable amount of evidence that in each breed there are particular strains of related individuals which have a higher degree of fertility than the average, and that flockmasters, by breeding from twin ewes and employing the services of twin rams, have been able permanently to increase the fertility of their stock.[1]

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[1] Iwanoff, "Sur la Fecondité de *Bison bonasus* × *Bos taurus*," *C. R. de la Soc. de Biol.*, vol. lxxv., 1913. See also other papers by Iwanoff (*C. R. de la Soc. de Biol.*, vol. lxx., 1911 ; *Biol. Cent.*, vol. xxxi., 1911 ; and *Zeitsch. f. ind. Abst. u. Vererbungslehre*, vol. xvi., 1916).

[2] See Suchetet, "Problèmes Hybridologiques," *Jour. de l'Anat. et la Phys.*, vol. xxxiii., 1897. Dewar and Finn, *The Making of Species*, London, 1909.

[3] Iwanoff, "Untersuchungen über die Unfruchtbarkeit von Zebröiden," *Biol. Cent.*, vol. xxv., 1905. "De la Fécondation Artificielle chez les Mammifères," *Arch. des Sciences Biologiques*, vol. xii., 1907.

[4] Morgan, *Experimental Zoology*, New York, 1907. See also *Heredity and Sex*, New York, 1913.

[5] The Leicester breed of sheep is characterised by a relatively low fertility, and this is said to be due to the preference that was shown to large single lambs at the time when high prices ruled, and the consequent discarding of ewes which bore twins. See Wallace (R.), *loc. cit.*

The inheritance of fertility in man and also in thoroughbred horses has been investigated statistically by Karl Pearson and his biometrical collaborators,[2] to whose memoir the reader is referred for a full discussion of the mathematical details and the conclusions which are arrived at. It is there shown, among other facts, that the woman inherits fertility equally through the male and female lines. Among thoroughbred race-horses the fecundity was first ascertained (*i.e.* the ratio of foals surviving to be yearlings to the total number of foals possible under the given conditions), and the following general conclusions were afterwards reached: (1) Fecundity is inherited between dam and daughter, and (2) Fecundity is also inherited through the male line, *i.e.* the sire hands down to his daughter a portion of the fertility of his dam. Thus fecundity, which is, of course, a latent character in the male, was measured for a horse and for his sire, and was found to be strongly inherited.

More recently Rommel and Phillips[3] have shown mathematically that there is an actual correlation between the size of the litter in two successive generations of Poland China sows, the productiveness being a character which is transmitted from mother and daughter.

On the other hand, Pearson,[4] from studying Weldon's records of mice-breeding experiments, failed to find a sensible parental correlation in regard to the size of the litters. Pearl and Surface,[5] as a result of a statistical investigation on egg-production in Barred Plymouth Rock fowls, found no evidence of the inheritance of fecundity so long as simple mass selection was practised. For this breed the capacity for egg-producing was not increased by this method, but tended rather to be diminished.

Pearl next started to analyse his results on the assumption that Mendelian factors might exist which were themselves concerned with different degrees of fertility. He found that the winter egg-production bore a direct relation to the total egg-production throughout the year. An average winter output of less than thirty eggs he found it useful to denote by one factor (L). This was ascertained to be dominant over the allelomorph (*l*) which is present in fowls laying no winter eggs. It is not sex-linked. A second fecundity factor (M) denotes a winter egg-production of more than thirty (even up to ninety) provided that it is present along with the first factor (L). Without it the egg-production is still less than thirty. This second factor (M) is sex-linked since it is carried only by ova which give rise to males. The high egg-production, therefore, is transmitted by the cock whose female offspring manifest it in the next generation.[1] By acting on this hypothesis Pearl was able substantially to increase the productivity of the Barred Plymouth Rock fowls, and although the theory has been criticised it must be admitted that it is extremely difficult to explain the results in any other way. As to what precise physiological signification is to be attached to a factor for fecundity is a point which we are not yet in a position to discuss, but the conception is not necessarily more difficult than that of any other kind of Mendelian factor.

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[1] Marshall, "Fertility in Scottish Sheep," *Trans. Highland and Agric. Soc.*, vol. xx., 1908.

[2] Pearson, Lee, and Bramley-Moore, "Mathematical Contributions to the Theory of Evolution: VI, Genetic (Reproductive) Selection, Inheritance of Fertility, etc.," *Phil. Trans.*, A., vol. cxcii., 1899.

[3] Rommel and Phillips, "Inheritance in the Female Line of Size of Litter in Poland China Sows," *Proc. Amer. Phil. Soc.*, vol. xlv., 1907.

[4] Pearson, "On Heredity in Mice, from the Records of the late W. F. R. Weldon," *Biometrika*, vol. v., 1907.

[5] Pearl and Surface, "Data on the Inheritance of Fecundity obtained from the Records of Egg Production, etc.," *Maine Agric. Exp. Station Bulletin* No. 166, Maine, 1909. Pearl, "A Biometrical Study of Egg Production in the Domestic Fowl," *U.S. Dept. of Agric., Bureau of Animal Industry, Bulletin* No. 110, Washington, 1909.

CERTAIN CAUSES OF STERILITY

A detailed account of the various pathological conditions which are capable of inducing sterility is outside the scope of this work. The medical publications dealing with the subject form a very considerable literature,[2] while the causes of sterility in animals are discussed, though somewhat unsatisfactorily, in many of the veterinary text-books. It may not be out of place, however, to refer briefly to certain of the conditions which are known to induce sterility in man and also in animals.

In the case of the male an incapacity to procreate is due either to impotence (*i.e.* inability to perform the sexual act), or to sterility (using the term in the more restricted sense, implying an absence of spermatozoa). Impotence may result from (1) absence of sexual desire, (2) absence of the power of erection and consequent intromission, (3) absence of the power of ejaculating the seminal fluid into the vagina, and (4) absence of the ability to experience pleasure during the act of coition, and at the time of the emission of the semen. Or, according to another classification, the causation of impotence may be either anatomical, physiological, pathological, or psychological. Among the anatomical causes may be mentioned defects and deformities in the penis. The physiological and pathological causes include incomplete erections, premature ejaculations, diseases of the brain and spinal cord (and more particularly of the centres for the performance of the sexual act), besides such diseases as albuminuria, or prolonged diabetes. The psychological causes include fear, repugnance, want of confidence, etc.[1]

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[1] Pearl, "The Mode of Inheritance of Fecundity in the Domestic Fowl," *Jour. of Exp. Zool.*, vol. xiii., 1912. See also papers in *Amer. Nat.*, vols. xlv., xlvi., xlix., and l., 1911-16. For Castle's criticism see *Amer. Nat.*, vol. xlix., 1915. For work on seasonal distribution in egg-production, see Pearl and Surface, *U.S. Dept. of Agric.*, *Bureau of Animal Industry*, *Bulletin* 110, Part 2, 1911. For further experiments, etc., on fecundity in fowls see recent papers by Pearl, Curtis, etc., in *Biol. Bull.*, *Jour. of Agric. Research*, *Arch. f. Entwick.-Mech.*, and various American journals. See also Goodale and M'Mullen, "The Bearing of Ratios on Theories of the Inheritance of Winter Egg Production," *Jour. of Exp. Zool.*, vol. xxviii., 1919.

[2] Müller (P.), *Die Unfruchtbarkeit der Ehe*, Stuttgart, 1885. This work contains a bibliography.

Complete sterility, *i.e.* inability to procreate owing to the absence of fertile semen, is due to various causes, and may be either congenital or acquired. Congenital sterility occurs when the testicles are never developed, or are so imperfectly developed that they fail to produce ripe spermatozoa. In cases of incomplete descent of the testicles fertility is rare, but it may exist for a short time as in young men from twenty to twenty-three years of age. Acquired sterility results from the various diseases to which the generative organs are subject, such as tubercle, syphilis, attacks of inflammation, urethral stricture, epididymitis, prostatic enlargement or diminution, etc.[2]

A more special cause of sterility in men is one which operates in the case of workers with radium or the Röntgen rays. Several years ago Albers-Schönberg[3] noticed that the X-rays induced sterility in guinea-pigs and rabbits, but without interfering with the sexual potency. These observations have been confirmed by other investigators,[4] who have shown, further, that the azoöspermia is due to the degeneration of the cells lining the seminal canals. In men it has been proved that mere presence in an X-ray atmosphere incidental to radiography sooner or later causes a condition of complete sterility, but without any apparent diminution of sexual potency.[5] As Gordon observes, for those working in an X-ray atmosphere adequate protection for all parts of the body not directly exposed for examination or treatment is indispensable, but, on the other hand, the X-rays afford a convenient, painless, and harmless method of inducing sterility, in cases in which it is desirable to effect this result.[1]

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[1] Corner, *Diseases of the Male Generative Organs*, London, 1907.

[2] Corner, *loc. cit.*

[3] Albers-Schönberg, "Ueber eine bisher unbekannte Wirkung der Röntgenstrahlen auf den Organismus der Tiere," *Münchener med. Wochenschr.*, No. 43, 1903.

[4] See Gordon, "Diseases caused by Physical Agents," Osler's *System of Medicine*, vol. i., London, 1907. See also Regaud and Dubreuil, "Action des Rayons de Röntgen sur la Testicule de la Lapin," *C. R. de la Soc. de Biol.*, vol. lxiii., 1907.

[5] Brown and Osgood, "X-Rays and Sterility," *Amer. Jour. of Surgery*, vol. xviii., (April) 1905.

The various causes of sterility in women are discussed at considerable length by Kelly,[2] as well as by other writers[3] on gynæcology. Kelly mentions the following conditions as likely to be found associated with sterility: Gonorrhœal infection of Skene's or Bartholin's gland, stricture of the vagina or cervix, the presence of a uterine polyp, a uterine fibroid tumour, a parovarian cyst, or a nodular salpingitis (from gonorrhœa or tuberculosis), atresia of the uterine tube (from inflammation), and the existence of ovarian adhesions. These, and other causes of sterility, and the methods of treatment to be adopted, are fully dealt with by Kelly.

Sterility in animals, as in man, is brought about by a variety of causes,[4] some of which are incurable, but others, such as constriction of the os uteri, are capable of treatment. In the case of cattle great difficulty is often experienced in getting the cows to breed after attacks of contagious abortion, and this is said to be due to an acid condition of the vaginal mucous membrane. In order to remedy this, injections of dilute solutions of bicarbonate of soda are employed and are found to be effective. Others recommend that the uterus should be injected with solutions of perchloride of mercury.[5]

Sterility in mares and cows and other animals is often due to structural or functional defects in the vagina, os uteri, or cervix. These may sometimes be overcome by resorting to artificial insemination, the methods of which are described below.[6]

Furthermore, sterility among cows may be contagious owing to the disease known as infectious granular vaginitis, which is primarily an acute inflammation of the vulva and vagina. It is commonly communicated by a contaminated bull in which the penis and sheath are affected. Similarly a bull may become diseased by serving an infected cow, and in this way vaginitis may spread through an entire herd. During recent years contagious sterility has been very common in Switzerland and Germany, and there is evidence of its existence in England. Antiseptic disinfection is useful, but experience has shown that even when treated infectious vaginitis often runs a prolonged course. Nevertheless, a complete cure usually takes place after some months, this recovery being indicated by the cessation of the muco-purulent discharge and the recurrence at normal intervals of the œstrous periods.[1]

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[1] Gordon, *loc. cit.* It has been shown also that the Röntgen rays may induce degeneration of the follicles, corpora lutea, and interstitial cells in the ovaries and cause sterility in the female. See Bouin, Ancel, and Villemin (*C. R. de la Soc. de Biol.*, vol. lxi., 1906), Bergonié and Trabondeau (*C. R. de la Soc. de Biol.*, vol. lxii., 1907), and Specht (*Arch. f. Gynäk.*, vol. lxxviii., 1907).

[2] Kelly, *Medical Gynecology*, London, 1908.

[3] See especially Duncan, *Sterility in Women*, London, 1884, and Müller, *loc. cit.* Duncan states his opinion that probably ten per cent. of the marriages in Great Britain are sterile.

[4] Fleming, *Text-book of Veterinary Obstetrics*, London, 1878.

[5] Wallace (R.), *loc. cit.* According to Knowles ("Sterility of Mares and Cows," *Amer. Veterinary Review*), "sub-acute and chronic cervical hyperæmia are probably the most frequent and fruitful causes of temporary sterility, due in an astonishingly large number of instances to continually recurring abortions."

[6] Constriction of the os uteri in cows may often be remedied by the employment of a large probe followed by the finger, or better still by a specially devised instrument known as a dilator. See Wallace (R.), *loc. cit.*

Deficient, excessive, or unfavourable nutrition, change of environment, in-breeding, etc., as sources of infertility, have been already discussed. (For persistence of corpus luteum as a cause see p. 373.)

Sterility may also be induced experimentally in animals by drugs or toxic substances. Rats treated with alcohol show abnormal sperm formation or atrophy of the seminiferous tubules. Guinea-pigs similarly treated have smaller litters and degenerate young. After administering thorium to newts the fertilised ova only partially develop.[2] Quinine sulphate when fed to laying ring-doves reduces the amount of yolk in the egg besides decreasing the deposition of albumen,[3] and other instances of a similar kind might be quoted, illustrating the susceptibility of the reproductive organs to the action of abnormal substances.

Artificial Insemination as a Means of Overcoming Sterility

Artificial insemination as a means of overcoming certain forms of sterility has been employed by various medical men from Hunter's time downwards. In the case treated by Hunter himself,[4] the husband of the woman experimented upon was affected with hypospadias. The semen was injected into the vagina, conception followed, and a child was afterwards born. Sims[5] recorded a case of a woman who suffered from dysmenorrhœa and a deformed uterus, and who had been married for nine years without having children. Artificial insemination was resorted to, pregnancy ensued, and a child was born in due time. Numerous other cases are cited by Heape[6] and Iwanoff,[7] to whose papers the reader is referred for bibliographies of the subject.

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[1] McFadyean, "Sterility in Cows," *Jour. Royal Agric. Soc.*, vol. lxx., 1909.

[2] See Hammond, *loc. cit.*, 1921.

[3] Riddle and Anderson, "Studies on the Physiology of Reproduction in Birds," VIII., *Amer. Jour. of Physiol.*, vol. xlvii., 1918.

[4] This case is described by Home, *Phil. Trans.*, 1799. (See p. 176, Chapter V.)

[5] Sims, *Notes Cliniques sur la Chirurgie Utérine*, Paris, 1866.

[6] Heape, "The Artificial Insemination of Mammals, etc.," *Proc. Roy. Soc.*, vol. lxi., 1897.

[7] Iwanoff, "De la Fécondation artificielle chez les Mammifères," *Arch. des Sciences Biologiques*, vol. xii., 1907.

The method adopted by gynæcologists who have practised artificial insemination is to inject seminal fluid into the uterus by means of a syringe, the fluid in most cases being obtained from the vagina of the same individual shortly after coitus. In this way it has been found possible to overcome such structural defects as constriction or undue rigidity of the cervix or hypertrophy of the lips of the external os uteri. By modifying the method by which the semen is obtained, it has proved possible to induce pregnancy in cases of abnormal vaginal secretion where the spermatozoa are ordinarily killed before they can effect an entrance into the uterus, and in other cases where there is an inability on the part of the vagina to retain the semen after coitus.

Artificial insemination has frequently been practised on mares with a view to overcoming certain forms of sterility, and considerable success has been attained. "Such defects as flexion or constriction of the canal of the cervix; rigidity of the cervix; hypertrophy of the lips of the external os, and the formation of false membranes which may effectually close the orifice; inability to retain spermatozoa in the vagina, owing to abnormal shortness of the organ or to violent muscular contraction after coitus; a want of sufficient muscular power; abnormal structure or size of the cervix or os uteri, which prevent the free action of the functions of the cervix; occlusion of the os owing to spasmodic contraction of the muscles of the cervix during coitus; abnormal or excessive vaginal secretions, which may kill or deleteriously affect the spermatozoa, etc., may be overcome by artificial insemination."[1] Heape, and more recently Iwanoff,[2] have cited numerous cases in which mares have been got in foal successfully by artificial insemination.

The actual methods employed are described by these writers.[3] The most usual plan is to allow the stallion to serve the mare in the ordinary way, and then, immediately afterwards, to insert a syringe into the vagina, and draw up into it some of the seminal fluid which is caused to collect in a depression or pocket made in the vaginal floor by the pressure of the finger tips. The same mare can then be inseminated by injecting the fluid so obtained into the uterine cavity, or the semen can be utilised for impregnating other mares. Another method is to collect the semen in gelatine capsules which are placed in the vagina before coitus, and then, when they have been filled, to close their lids and insert them in the interior of the uterus, where the heat of the body gradually melts the gelatine and sets free the spermatozoa. By such means as this several mares may be impregnated as a result of one service by a stallion. In some cases pieces of sponge have been employed instead of gelatine capsules.[1]

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[1] Heape, "The Artificial Insemination of Mares," *Veterinarian*, 1898. In the writer's experience incapacity to retain the semen after service is a common cause of sterility. It is sometimes possible to catch the fluid as it is evacuated from the vagina with a beaker, and then to inject it through the os uteri.

[2] Iwanoff, *loc. cit.* This important memoir, besides containing descriptions of the author's own experiments, gives a very full account of the literature of artificial insemination. See also Iwanoff, *Jour. of Agric. Sci.*, vol. xii., 1922.

[3] See also a booklet edited and published by Huish *The Cause and Remedy for Sterility in Mares, Cows, and Bitches*, London.

Artificial insemination has been of considerable use also in remedying sterility in cows as well as in dogs.[2]

Several investigators by employing artificial insemination have been successful in getting crosses between animals belonging to varieties in which the disparity in size is so great that coitus between them is difficult or impossible. Thus, Plönnis[3] in 1876 successfully inseminated a lap-dog with the semen of a setter, and obtained a pup which in most of its points resembled its father. Allbrecht[4] performed a similar experiment and obtained a similar result. More recently Heape[5] has described some experiments carried out by Millais, in which bloodhounds were inseminated with spermatozoa obtained from Basset hounds (a much smaller breed), litters of cross-bred pups being produced.

Iwanoff[6] has recorded an experiment in which he successfully inseminated a white mouse with the spermatozoa of a white rat. Two hybrid young ones were produced after a pregnancy lasting twenty-seven days. They were intermediate in size between rats and mice. This is the first record of a cross being obtained between two species so different in size as the rat and the mouse, coitus between them being practically impossible. Furthermore, Iwanoff has successfully employed artificial insemination to obtain hybrids between horses and zebras (a cross which is often difficult to get by the normal method owing to the liability of the animals to refuse service).

The problem of preserving spermatozoa alive in artificial media is one which has only recently been investigated systematically. It is evident that were one in a position to send semen to a distance

[1] For further information and practical details see Iwanoff, *Die Künstliche Befruchtung der Haustiere*, Hannover, 1912. For experiments with fowls see Iwanoff, "Expériences sur la Fécondation Artificielles des Oiseaux," *C. R. de la Soc. de Biol.*, vol. lxxv., 1913.

[2] See Huish, *loc. cit.*

[3] Plönnis, "Künstliche Befruchtung einer Hünden, etc.," *Inaug.-Dissert.*, Rostock, 1876.

[4] Allbrecht, "Künstliche Befruchtung," *Wochenschr. f. Thierheilkunde und Viehzucht*, Jahrg. xxxix.

[5] Heape, "The Artificial Insemination of Mammals," *Proc. Roy. Soc.*, vol. lxi., 1897.

[6] Iwanoff, *loc. cit.*

and then successfully inseminate, it would be a very great economic advantage to the breeding industry.

That the spermatozoa of the bull may survive for as long as twelve days within the removed testicle if the latter be kept at a temperature a little above freezing point, has been shown by Iwanoff. Outside the tissues of the animal Iwanoff found that spermatozoa may preserve their motility for some hours in solutions of sodium chloride, barium chloride, and potassium nitrate, but the exact lengths of time do not appear to be stated, neither is the temperature recorded. Ochi[1] and Sato[2] confirmed these results and found further that the artificial medium was improved if an isotonic solution of glucose was added. They state also that oxygen in moderate amounts is helpful in preserving the life of the spermatozoa. Yamane[3] gives an account of successful experiments with injecting horse's semen diluted with physiological salt solution and glucose, but the semen was used immediately after dilution and not kept in the artificial medium. Wolf,[4] working with rabbits' semen, found that for maintaining the vitality of the spermatozoa two conditions were necessary; first, the reaction of the fluid should be as near that of normal blood as possible; and secondly, a sufficiency of "buffer salts" should be present in order to prevent any great change in reaction due to metabolism of the spermatozoa themselves. Wolf's general conclusion is that with "the combination of a properly balanced physiological saline solution with an isotonic glucose solution, a sufficiency of oxygen and a careful regulation of the hydrogen-ion concentration, it is quite possible to keep these cells in a condition in which motility can be restored on raising to body temperature, provided that in the interval they are kept at a temperature near 0° C." In such an environment the spermatozoa could retain their potential motility for nine days.

ABORTION

Abortion is often an important factor in determining a low fertility, but its frequency of occurrence shows a considerable range of variation.

With women the frequency of abortion to birth at full term is said to be from one in five to one in ten.[1] According to the records of Franz[2] for the maternity hospital at Halle, the percentage of cases in which abortion occurred was 15·4. Williams[3] expresses the opinion that in ordinary private practice every fifth or sixth pregnancy usually ends in abortion, and that the percentage would be considerably increased if one reckoned the early cases in which there is a profuse loss of blood following a retardation of the menstrual period, the actual fact of abortion being often obscured.

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[1] Ochi, "Physiological Studies on Spermatozoa, especially its Life Duration," *Actæ Scholæ Med.*, Univ. Imp. in Kioto, vol. i., 1916.

[2] Sato, "On the Life Duration of the Horse Spermatozoa outside of the Body," *Actæ Scholæ Med.*, Univ. Imp. in Kioto, vol. i., 1916.

[3] Yamane, "Studien über die Physikalische und Chemische Beschaffenheit des Pferdespermas, etc.," *Jour. of Coll. Agric.*, Hokkaido Imp. Univ., vol. ix., 1921.

[4] Wolf, "The Survival of Motility in Mammalian Spermatozoa," *Jour. of Agric. Science*, vol. xi., 1921.

Excepting in the case of sheep, there are no satisfactory data on which to estimate the frequency of abortion among the different kinds of domestic animals, but there can be no doubt that it is of common occurrence, and that it occasions much loss to breeders. For various varieties of English sheep Heape[4] found that the percentage of abortion experienced by 300 flockmasters varied from nothing to 23·75, while the percentage for 85,878 ewes was 2·39. The statistics showed that Dorset Horn and Lincoln breeds suffered most from abortion, the losses from this cause being respectively 4·11 per cent. and four per cent. The Southdown breed were found to occupy an intermediate position (the percentage of abortion being 2·86 per cent.), while the other breeds investigated showed a smaller percentage of abortion. Among Scottish breeds the percentage of aborting ewes does not generally exceed two per cent., as far as could be ascertained; but with Blackfaced ewes it may be as much as five, or even a considerably higher number, as a consequence of any special adverse circumstance.[5] It is possible, however, that the percentages of abortion are actually somewhat higher than they appear, since its occurrence during the early stages of pregnancy is not readily detected, and consequently some of the ewes which were entered in the statistical returns as barren may in reality have aborted.

Among cattle in Great Britain the frequency of abortion, according to Heape,[6] is not less than ten per cent. of the total number of animals selected for breeding, and there can be no doubt that in certain districts it is often very much higher, especially where contagious or epidemic abortion occurs. Heape states further that from ten to twelve per cent. of abortion is not unusual in herds in which no contagious abortion is proved to exist.

There are no data available on which to compute the frequency of occurrence of abortion among horses, but the experience of breeders shows that the losses arising from this cause are very considerable, and that they are greatest amongst the better-bred animals. One of the earlier reports of the Royal Commission on Horse-Breeding stated that in this country in any given year no less than forty per cent. of the mares chosen for breeding fail to produce foals, but to what extent this result is due to sterility or how far it may be ascribed to abortion does not appear to have been ascertained.

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[1] Kelly, *loc. cit.*

[2] Franz, "Zur Lehre des Aborts," *Hegar's Beiträge*, vol. i., 1898.

[3] Williams, *Obstetrics*, London, 1904.

[4] Heape, "Abortion, Barrenness, and Fertility in Sheep," *Jour. Royal Agric. Soc.*, vol. x., 1899.

[5] Marshall, "Fertility in Scottish Sheep," *Trans. Highland and Agric. Soc.*, vol. xx., 1908.

[6] Heape, *The Breeding Industry*, Cambridge, 1906.

The causes of abortion are diverse, and may be mechanical, psychological, physiological, or pathological. Deliberate abortion among civilised European nations is a criminal offence punishable by law, but nevertheless is not infrequently carried out. In Oriental countries and among savages abortion is practised more openly. The more usual means are drugs (ergot, ethereal oil of juniper, yew, turpentine, camphor, cantharides, aloes, etc.),[1] but none of these is infallible, and owing to their toxic properties their use is often accompanied by danger. Haddon[2] says that among the Eastern Islanders of the Torres Straits abortion is procured by the leaves of the shore convolvulus and certain other plants. Also the old women give the younger women young leaves of the argerarger (*Callicarpa sp.*), a large tree with inedible fruit, and bok, a large shrub. When a woman's body is saturated with the juice from the leaves, she is believed to be proof against fecundity, and can indulge in sexual intercourse without fear of becoming pregnant. Probably the toxic substances introduced cause abortion at very early stages of pregnancy, or even inhibit pregnancy at the very outset. Abortion is sometimes procured by purely mechanical means—*e.g.* blows, massage, hot injections,[3] carrying heavy loads,[4] etc. But although mechanical and psychological influences, both voluntary and involuntary, play a part in bringing about abortion, they are probably less frequently concerned in the process than pathological conditions existing either in the embryo or in the maternal organism.

Among the causes of abortion in women Kelly[5] mentions hæmorrhage of the chorion, imperfect vascularisation of the amnion, hydatiform degeneration of the chorion, circulatory disturbances caused by heart lesions in the mother, various infections of the mother (notably syphilis), psychic disturbances, and excessive cohabitation, acute poisoning (by alcohol, phosphorus, lead, etc.), and various diseases of the generative organs, such as endometritis, decidual inflammation, polypoid thickening, etc. It is stated that the excitability of the nerve centres which control the movements of the uterus and the tendency to uterine congestion are greatest at the epochs which would have been menstrual periods if pregnancy had not occurred, and consequently that abortion is especially common at these dates.[1] The membranes are usually cast off with the fœtus, but the decidua is said in some cases to remain, and to regenerate a normal uterine mucosa. The expulsion of the fœtus and membranes is accompanied by "pains" comparable to those occurring in normal parturition, the two processes having a general similarity, which is closer if abortion takes place in the later part of pregnancy. There is generally also a considerable loss of blood. After the expulsion the hæmorrhage and pains cease, and a process of puerperal involution sets in.

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[1] Bloch, *loc. cit.*

[2] Haddon, *loc. cit.*

[3] Bloch, *loc. cit.*

[4] Haddon, *loc. cit.*

[5] Kelly, *loc. cit.* See also Oliver, "The Determinants of Abortion," *Brit. Med. Jour.*, 30th November 1907.

In horses abortion is probably most frequent during the period from the sixth to the ninth week of pregnancy. This is explained by Ewart[2] as being due to the fact that about this time the embryo loses its primitive attachment to the uterus before acquiring its more permanent connection by means of the allantoic villi, which are only beginning to be numerous. The yolk-sac, which in the marsupial is the organ of fœtal nourishment throughout the whole of pregnancy, in the case of the horse ceases to provide a sufficient supply at about the end of the seventh week; but the horse embryo, instead of being born at this period, like the marsupial, acquires new and more efficient structures in the allantoic villi. "At the end of the third week of gestation, when the reproductive system passes through one of its periods of general excitement, about one-fourth of the embryonic sac probably adheres to the uterus; but at the end of the sixth week, when another wave of disturbance arrives, all the grappling structures are at one pole. Hence there is probably more chance of the embryo 'slipping' at the end of the sixth than at the end of the third week. About the end of the seventh week the supply of nourishment by means of the yolk-sac is coming to an end, and there is perhaps still about this time an hereditary tendency for the embryo to escape. Unless the new and more permanent nutritive apparatus is provided, unless a countless number of villi rapidly sprout out from the allantois, the embryo will die from starvation during the eighth week, and in a few days be discharged. It may therefore be taken for granted that there is a certain amount of danger at the end of the third and sixth weeks, but that the most critical period is about the end of the seventh or beginning of the eighth week; for unless the villi appear in time, and succeed in coming into sufficiently intimate relation with the uterine vessels, the developmental process is of necessity for ever arrested."

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[1] Galabin, *Manual of Midwifery*, 6th Edition, London, 1904.

[2] Ewart, *A Critical Period in the Development of the Horse*, London, 1897.

Ewart discusses briefly the external conditions and circumstances which are likely to lead to abortion, and provides some useful practical hints as to the best way to treat mares in order to prevent them from "slipping foal." He remarks that the horse is a peculiarly high-strung, nervous animal, and is easily affected by sudden changes in its surroundings, especially during the breeding season. Such changes are, no doubt, often responsible for setting up disturbances in the nervous system, and so inducing abortion, more particularly at that period of development at which the fixation of the embryo to the uterine wall is relatively insecure.

Abortion in cows is said to be commonest during the first month of pregnancy. According to Wallace[1] the usual causes are the following: (1) Eating ergotised grass; (2) injury due to horning by other cattle, hunting by dogs, or shaking and bruising in travelling, etc.; (3) physical strain, resulting from walking over too soft land, etc.; (4) very cold or foul water, or frozen turnips, etc.; (5) superpurgation, whether occurring naturally or as a consequence of dosing by physic; (6) contagion from other cows affected by epidemic abortion. This is said to be the commonest and at the same time the most dangerous cause of abortion.

Bang[2] has shown that contagious, epidemic, or epizoötic abortion in cattle is due to a specific bacillus which he has been able to isolate and cultivate in oxygenated glycerine-bouillon or serum-gelatine agar. The germ causes the formation of a brownish-yellow exudate between the chorion and the mucous membrane of the uterus, and more particularly around the cotyledons, but the affected area may be considerably greater.[3] Bang has shown experimentally that the germs may be carried to the seat of the disease by the blood after intravascular injection, and furthermore, that they can be absorbed through the alimentary canal. Thus, after administering some bouillon culture to a cow, the placenta was found covered with typical exudate rich in bacilli. It is probable, therefore, that entrance through the alimentary canal is the most frequent way by which the disease is spread. There is some experimental evidence that cows may acquire immunity to the disease, at least temporarily. Investigations show also that mares, sheep, goats, dogs, and guinea-pigs may be infected with the bacillus experimentally, but in all probability the disease is ordinarily confined to cattle. The abortion microbe is stated to be oval or rod-shaped, between one and two microns in length, and non-motile. It sometimes occurs singly, but in many places the bacilli are collected in dense groups or colonies. The microbe associated with abortion outbreaks in sheep is said to be a vibrio and therefore totally different.[1] It has been isolated and used experimentally to infect pregnant ewes. Pregnant cows, however, cannot be infected by it. Horses and swine may also suffer from abortion of an epizoötic nature.

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[1] Wallace (R.), *loc. cit.* Wallace states that after abortion in cattle the placenta adheres to the cotyledons, and should be removed artificially; otherwise it is liable to undergo a process of rotting, sometimes resulting in septicæmia and death. See Fleming, *Veterinary Obstetrics* (Craig's Edit.), London, 1912.

[2] Bang (B.), "Infectious Abortion in Cattle," *Nat. Vet. Soc.*, Liverpool, 25th July 1906.

[3] *Report of the Departmental Committee appointed by the Board of Agriculture and Fisheries to inquire into Epizoötic Abortion*, London, 1909. According to this Report, nothing more than a quite subsidiary rôle in the spread of the disease can now be referred to the bull. For further information and references see Surface, "The Diagnosis of Infectious Abortion in Cattle," *Report of Kentucky Exp. Stat.*, 1912; "Notes on Infectious Abortion in Cattle," *Science*, vol. xxxvi., 1912; and "Bovine Infectious Abortion Epizoötic among Guinea-Pigs," *Jour. of Infectious Diseases*, vol. xi., 1912; also McFadyean, "Epizootic Abortion of Cattle," *Jour. Comp. Path. Ther.*, 1921.

The external use of antiseptics is said to prevent the spread of contagious abortion by means of disinfection, but isolation is the most effective method.[2] Vaccine treatment is an efficacious preventive.

The causes of abortion in sheep are dealt with at some length by Heape in the paper already referred to.[3] Statistical evidence shows that an excessive proportion of shearling ewes in a flock is associated with a relatively high percentage of abortion, and that ewes of particular breeds in certain districts, or run on certain subsoils, are more liable to abortion than the average for the breed in question. Thus Lincoln sheep run on the Wolds suffer much more from abortion than sheep of the same breed in other districts. The Southdown and Hampshire Down statistics show that a heavy rainfall during gestation is associated with a high degree of abortion. Over-exertion (as from jumping ditches), fright (from strange dogs or shooting), are usually credited with producing abortion in sheep, but Heape remarks that such causes are not truly responsible unless the ewes are in a susceptible condition. The main conclusion reached is that the food and the resulting condition of the ewes are the principal factors which influence the percentage of abortion. Unsuitable food, causing indigestion or other ailments, and poor food, resulting in bad nutrition, are held to be mainly responsible. Heape states, however, that it is not the kind of food so much as the condition of the food which is most liable to be at fault, while the schedules show clearly that a poor condition of ewes during gestation is associated with a relatively high percentage of abortion. "Sheep-stained" pasture (*i.e.* pasture grown with the aid of sheep manure or on which sheep have been run for a considerable time previously) is credited with causing abortion, and there is strong evidence in support of this view in cases where rank or over-stimulated growth results.[1]

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[1] Heatley, "Abortion in Sheep," *Board of Agric. Dept. Committee Report.* Printed by the Suffolk Sheep Society, Bury St. Edmunds, 1914.

[2] Board of Agriculture Leaflet, No. 108, 1904.

[3] Heape, "Abortion, Barrenness, and Fertility in Sheep," *Jour. Royal Agric. Soc.*, vol. x., 1899. See also Fleming, *loc. cit.*

As already noted, the Dorset Horn and Lincoln breeds of sheep suffer most from abortion.[2] In the case of the former this may result partly from in-breeding, since Dorset Horn ewes served by Hampshire Down rams are less liable to "slip lamb" than those served by rams of their own breed. It is possible, therefore, that the abortion may be due to a want of vitality on the part of the developing embryo, the cross-bred young possessing a superior vigour. Abortion among Lincoln sheep has been known to reach thirty, forty, or even fifty per cent., and so to assume an epidemic form. Wortley Axe,[3] who reported on an outbreak of abortion among the Lincolnshire flocks in the season of 1882-83, was disposed to attribute it to debility, arising largely from foot-rot and exposure to cold winds and heavy continuous rains, as well as to the feeding of the ewes on unripe, watery roots and unwholesome, filth-laden shells. Heape has suggested that abortion on the Wolds arises partly from the practice of unduly crowding the ewes on turnip fields. As already mentioned, a bacillus has been isolated from outbreaks of abortion in ewes, and has been used to infect other ewes for experimental purposes in the laboratory.

Hammond[4] has shown that atrophy of fœtuses *in utero* is a very common phenomenon in pigs as well as in domestic rabbits. It occurs at different degrees of embryonic development, and degenerate fœtuses of different sizes and in a mummified condition are commonly found in the same uterus. Hammond counted the fœtuses in the uteri of twenty-two sows and found that for 100 eggs shed (shown by the corpora lutea) there were 67·4 normal fœtuses and 12·4 atrophic fœtuses (leaving 20·2 ova missing or unaccounted for). In domestic rabbits the proportion of degenerate fœtuses was closely similar. Degenerate fœtuses *in utero* have been recorded also for the following animals: mare, cow, sheep, goat, guinea-pig, hamster, rat, mouse, ferret, dog, cat, and mole. The proportion of atrophic fœtuses in wild rabbits is very much smaller than in tame ones, and Hammond draws the conclusion that the fertility of many domestic animals is limited by the number of discharged and fertilised ova which develop rather than by the number of ova which are shed. With regard to the cause of the fœtal atrophy Hammond has shown that it is not due to bacterial infection since the uteri are aseptic. He suggests that it may be brought about by adiposity, by in-breeding, or by a genetic "lethal factor" such as Kirkham[1] and others have shown probably to be the case with the homozygous yellow mice which are never brought forth alive but die *in utero* during implantation. The fœtal atrophy is not due to lack of room in the uterus, for this organ is capable of great expansion, and the distribution of the degenerate fœtuses is irregular and does not suggest that death was due to overcrowding. It is true, however, as Hammond has shown in pigs, that the size of the fœtus is roughly proportional to the extent of its membranes, and that the fœtal membranes of single lambs, which are as a rule larger than twins, extend to both horns of the uterus. It is also generally true that the average weight of the embryo increases as the size of the litter decreases, and that the larger and better nourished the mother the larger are the young. Nutrition is probably an important factor both in the size of the litter and in the sizes of the individuals, as experiments on various animals have shown, but there must be variation in the degrees of vitality inherent in the different fœtuses. Some perish more easily than others as is well shown in pigs, but even those which survive long enough to be born are often ill-nourished and under-sized and in striking contrast to other piglings of the litter. Hammond states that atrophy of the fœtuses begins in the blood-vessels, which first become congested and then break down. The fœtal membranes may remain alive for some days after the embryos have perished.

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[1] Abortion in sheep may result from more exceptional causes. Thus it is recorded that a large proportion of a certain flock of Cheviot ewes slipped lamb after a gale which blew down a number of Scotch fir trees, the abortion resulting, in the owner's opinion, from the animals eating the branches and bark. See Marshall, *loc. cit.*

[2] Heape, *loc. cit.*

[3] Wortley Axe, "Outbreak of Abortion and Premature Birth in the Ewe Flocks of Lincolnshire during the Winter and Spring of 1882-83," *Jour. Royal Agric. Soc.*, vol. xxi., 1885.

[4] Hammond, *loc. cit.*, 1913 and 1921. These papers contain further references.

THE INCREASE OF FERTILITY, A PROBLEM OF PRACTICAL BREEDING

Heape[2] has shown from statistical evidence that the amount of money invested in live stock in this country cannot be computed at very much less than £450,000,000, and this sum does not include the enormous capital spent on buildings, land, vehicles, and various accessories. The annual export of live stock from Great Britain in recent years has been tending steadily to increase, until it has reached a total value of £1,750,000. It is clear, therefore, that in this country the breeding industry occupies a position of no inconsiderable importance, and that the scientific study of the problems of breeding possesses a great national interest. Foremost among these problems is that which concerns itself with the factors that control fertility.

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[1] Kirkham, "The Fate of Homozygous Yellow Mice," *Jour. Exp. Zool.* vol. xxviii., 1919. Lethal factors have been described for various other organisms (*Drosophila*, maize, etc.). See Babcock and Clausen, *loc. cit.*

[2] Heape, *The Breeding Industry*, Cambridge, 1906.

Despite its comparative prosperity, it is evident that the breeding industry suffers annually from no inappreciable loss. Allusion has been made to the losses sustained by breeders owing to the occurrence of abortion in domestic animals. Sterility, whether persistent or temporary, is responsible for a greater reduction of profit. The prevalent barrenness among the better class of Shire mares has been already referred to, while incapacity to breed is perhaps still commoner among Thoroughbreds. As already mentioned, the Royal Commission on Horse-Breeding found that no less than forty per cent. of the mares chosen for breeding in any given year failed to produce offspring. Recent statistical evidence for heavy horses shows an even larger proportion of mares failing to breed.[1] Moreover, there is evidence that in certain districts of India the percentage of sterility is as high or higher than in this country.[2] Among cattle the average loss from sterility and abortion (together with mortality of calves) is estimated by Heape[3] to be at least fifteen per cent., while it is shown in the report (already referred to) issued by the Royal Agricultural Society on fertility in English sheep for the year 1899, that the proportion of sterile ewes was 4·71 per cent. out of a total number of 96,520, and this percentage does not include the ewes which aborted (see p. 651). In view of these facts, it is obvious, as Heape has pointed out, that any means by which sterility in domestic animals can be checked and their capacity to bear young increased, must be possessed of great commercial value.

The Birth-Rate in Man

It is now more than a century ago since Malthus[4] advanced his famous proposition that whereas population tends to increase in geometrical ratio, the means of subsistence increase only in arithmetical proportion. As a consequence of the acceptance of that doctrine, the political economists of the early Victorian period tended to see in over-population the most fruitful source of pauperism, disease, and crime, and the cause of increasing congestion in the future. That Malthus' predictions have not been verified is a matter of common knowledge, and the problem before the modern economist is not how to place a check on population generally, but rather how to secure that future generations shall be sufficiently recruited from that section of the population which is industrially capable, while at the same time to prevent indiscriminate propagation.

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[1] Marshall and Crosland, "Sterility in Mares, with Recommendations to Breeders of Heavy Horses," *Jour. of the Board of Agric.*, vol. xxiv., 1918.

[2] Ewart, *loc. cit.*

[3] Heape, *loc. cit.*

[4] Malthus, *An Essay on the Principles of Population*, 7th Edition, London, 1872.

There is abundant evidence that in most civilised countries at the present time the birth-rate (that is, the proportion of the children born to the population) is tending to decrease, while in some countries the actual population is diminishing. This decline in the birth-rate has been made the subject of statistical inquiries by Newsholme and Stevenson,[1] and Udny Yule.[2] These writers have shown that the observed fall is not simply a consequence of changes in the ages of the people, or in the proportion of married to single women, for allowing for such alterations as have occurred, the number of births per 100,000 of the population in England and Wales, for example, has dropped from 3236 in 1861 to 2729 in 1901. Yule concludes that "the main factor in the fall of the birth-rate has been a decrease in the fertility of married women: this fall has been proceeding at an accelerating speed."[3]

The decline in the birth-rate (so far as England and Wales are concerned) is not appreciably greater in the towns than in the rural districts. It is, however, especially marked in places inhabited by the servant-keeping class.[4] It appears to be greatest in those sections of the population which give evidence of the exercise of thrift and foresight, for Heron[5] has shown that the more cultured, prosperous, and healthy classes are producing fewer children than those belonging to a lower social status. Marriage fertility is on the whole graduated continuously from a very low figure for the upper and professional classes to a very much higher figure for unskilled labour.[6]

There is no direct evidence that this decline in the birth-rate is due to an increase of sterility, for congenital unavoidable sterility in either sex is rare. The inference has been drawn, therefore, that the decline is principally the result of deliberate volition in the regulation of the married state. Evidence that this inference is correct is provided by the Fabian Society, whose report indicates that the practice of limitation prevails with at least one-half, if not three-fourths, of all the married people of Great Britain. The statistics collected from other countries point in a similar direction. This is noticeably the case for New South Wales,

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[1] Newsholme and Stevenson, "The Decline of Human Fertility in the United Kingdom, etc.," *Jour. Royal Statis. Soc.*, 1906.

[2] Yule, "On the Changes in the Marriage and Birth-Rates, etc.," *Jour. Royal Statis. Soc.*, 1906.

[3] Yule, *The Fall of the Birth-Rate*, Cambridge, 1920. (With further references.)

[4] Sidney Webb, *The Decline in the Birth-Rate*, Fabian Soc. Tract, London, 1907.

[5] Heron, "On the Relation of Fertility in Man to Social Status, etc.," *Drapers' Company Memoir*, London, 1906.

[6] *The Population Problem, a Study in Human Evolution* (Oxford, 1922), is ably discussed by Carr-Saunders, who writes as follows: "It is forgotten that the reduction in the birth-rate may be that which economic conditions demand, and that it may of necessity have to begin with the upper classes. Though, therefore, differential fertility by producing unfavourable germinal changes is to that degree to be deplored, yet we have to remember that so far as quantity is concerned, failure to meet economic requirements might be a much greater misfortune."

Victoria, and New Zealand among the British Colonies, and for France among Continental nations. Indications pointing apparently in the same direction are to be observed in the United States, Germany (especially Saxony, and certain of the big cities), as well as in Belgium and Italy. The German rural population are apparently still unaffected, while the British and Irish Catholics are almost so, since any regulation of the married state is forbidden by their religion, but in other Catholic countries this prohibition does not appear to be so strongly insisted on, and is often altogether ignored. On the other hand, Udny Yule has shown that in some countries (*e.g.* Belgium before 1875) the fall in the birth-rate began at a time when artificial methods of contra-conception were not generally practised, and his general conclusion is that the recent decrease has not been effected mainly or solely by such a cause.[1]

To the political economist of seventy years ago the decline in the production of children would have been regarded as the fulfilment of an aspiration, but the modern economist takes a different view. He believes that a mere limitation of numbers cannot be a factor in the improvement of social conditions, and the student of Eugenics never tires of urging that the real danger before society is not over-multiplication, but multiplication of the unfit. As Sidney Webb has said: "Modern civilisation is faced by two awkward facts; the production of children is rapidly declining and this decline is not uniform, but characteristic of the more prudent, foreseeing, and restrained members of the community. . . . The question is whether we shall be able to turn round with sufficient sharpness and in time. For we have unconsciously based so much of our social policy—so many of our habits, traditions, prejudices, and beliefs—on the assumption that the growth of population is always to be reckoned with, and even feared, that a genuine realisation of the contrary position will involve great changes. There are thousands of men thinking themselves educated citizens to-day to whose whole system of social and economic beliefs the discovery will be as subversive as was that announced by Copernicus. We may at last understand what the modern economist means when he tells us that the most valuable of the year's crops, as it is the most costly, is not the wheat harvest or the lambing, but the year's quota of adolescent young men and women enlisted in the productive service of the community; and that the due proportion and best possible care of this particular product is of far greater consequence to the nation, than any other of its occupations."[2]

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[1] Yule, *loc. cit.* Pell has come to a similar conclusion, *The Law of Births and Deaths*, London, 1921.

[2] Sidney Webb, *loc. cit.* *Cf.* also Whetham, *The Family and the Nation*, London, 1909; and Inge, *Outspoken Essays*, London, 1920.

CHAPTER XV

THE FACTORS WHICH DETERMINE SEX[1]

"What was a question once is a question still."—Bacon.

A work upon the Physiology of Reproduction would be incomplete without some reference to the problem of sex-determination, and some account of the more recent attempts which have been made towards its solution. The question has been dealt with at length in several recent works, such as those by Morgan and by Doncaster, Correns and Goldschmidt, and Goldschmidt,[2] and the reader is referred to these treatises, especially the last, for further references and fuller information in regard to certain of the points discussed. It is hoped, however, that the present summary may prove useful if only as a supplement to the other volumes that have appeared, since certain important papers dealing with sex-determination and containing an account of experimental investigations have been published since the appearance of the works referred to, and these papers I have endeavoured to summarise here. Moreover, some of the more recent observations, and more particularly those relating to sex reversal, have necessitated a further revision of the conclusions previously arrived at.

Reproduction in organisms may occur by simple fission or budding, in which case it is said to be asexual, or it may involve the union of two conjugating cells, which in Metazoa and Metaphyta are specially differentiated for the purpose, and are known as ova and spermatozoa (see Child's work, p. 225, above). In some animals these two types of cell are produced by the same individual, which is then said to be hermaphrodite or monœcious, but such a condition is rare or absent altogether among the highest forms of life. In the vast majority of animals there are two sexes—that is to say, two kinds of sexual individuals, the male and the female, whose respective functions are to produce spermatozoa and ova. This condition is described as diœcious. Again, in a relatively small number of animals, of which the bee is a familiar example, there are three kinds of individuals—perfect females, imperfect females, and males. In a few insects there are even more than three kinds. Lastly, in certain of the lower animals the females can reproduce ova which are capable of developing into adult individuals without conjugating with spermatozoa. This method of reproduction is described as parthenogenetic (see p. 230).

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[1] With additions by Cresswell Shearer.

[2] Morgan, *Heredity and Sex*, New York, 1913. Doncaster, *The Determination of Sex*, Cambridge, 1914. Correns and Goldschmidt, *Die Vererbung und Bestimmung des Geschlechts*, Berlin, 1913. Goldschmidt, *Mechanismus und Physiologie der Geschlechtsbestimmung*, Berlin, 1920. See also Geddes and Thomson, *The Evolution of Sex*, Revised Edition, London, 1904; Thomson, *Heredity*, London, 1914; and Babcock and Clausen, *Genetics in Relation to Agriculture*, New York, 1918.

Among diœcious animals the two sexual individuals are generally produced in approximately equal numbers. Thus, in man the number of male births is only slightly in excess of the number of female births, the proportion varying very slightly in different countries,[1] while in those races in which the numerical proportion of the two sexes among the adult population is very unequal, inequality is due to a higher death-rate of children belonging to one sex. Thus among the Todas the pronounced preponderance of males over females results from the practice of female infanticide.[2]

Theories of sex determination may be conveniently arranged under three headings: (1) Those in which it is assumed that the sexual condition of the individual is determined subsequently to fertilisation and during embryonic or larval life; (2) those which assume that sex is established either at the moment of fertilisation or prior to fertilisation; and (3) those which limit sex-determination to no particular period, or which definitely assert that sex may be established at different periods of development in different animals.

(1) Theories which assume that Sex-determination takes place subsequently to Fertilisation

In tadpoles sex is apparently indeterminate until a relatively late stage of development, but it is said to be established at the time of metamorphosis. Born,[3] and subsequently Yung[4] and certain other investigators, have adduced evidence in support of the view that the sex is determined by the quantity and quality of the food supply. Thus they claimed that they could produce an excess of females by feeding the tadpoles upon a meat or fish diet. The conclusions of these authors, however, are hardly borne out by more recent researches, for Cuénot's experiments,[1] conducted on similar lines to those of Born and Yung, show a preponderance of males among tadpoles which were fed upon animal food, and an approximate numerical equality among those which received an exclusively vegetable diet. Moreover, the method adopted by Born for ascertaining the sex of the individual tadpoles during the period of metamorphosis seems to have been unsatisfactory, since it was based on the assumption that the ovary is always larger than the testicle, whereas this is not invariably the case. It is stated also that frogs' eggs from certain localities yield a higher percentage of females than those from other localities, and consequently that a disproportion of the sexes may exist under normal conditions; but this fact in itself does not show that sex is not determined by nutritive or other environmental influences, but may point to a directly opposite conclusion. But, as Morgan points out, if the natural disproportion between the two sexes is great, errors may easily creep into the experimental results.[2] Again, King's observations relating to sex-determination in Amphibians provide no evidence that either food or temperature are factors in this process.[3]

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[1] Bodio, "Movimento della Populazione," *Confronti Internazionali*, 1895.

[2] Punnett, "On the Proportion of the Sexes among the Todas," *Proc. Camb. Phil. Soc.*, vol. xii., 1904.

[3] Born, "Experimentelle Untersuchungen ueber die Entstehung der Geschlechtsunterschiede," *Breslauer ärztliche Zeit.*, 1881.

[4] Yung, "De l'Influence de la Nature des Aliments sur la Sexualité," *C. R. de l'Acad. des Sciences*, vol. xciii., 1881.

Since the early work of Born and Yung, however, many other observations of a more critical character have been made on the question of sex-determination in Amphibians. The most remarkable of these has been the recent work of Witschi.[4] A full summary of these observations down to the latter part of 1921 will be found in Crew's[5] paper. It would seem that in the frog while the chromosome constitution may determine sex at fertilisation, in some instances this is clearly overridden during subsequent development, which results in the production of "somatic" males or masculinised females. The mechanism by which the female is transformed is one which acts through the internal secretions of the gonads.

Thus it would seem that in Amphibians sex is not definitely fixed at the time of fertilisation. In the case of the lamprey, somewhat similar conclusions have been arrived at by Okkelberg[1] in an important paper. In this animal the germ-cells of each germ gland are seen at a very early stage to be of two kinds, one set showing a tendency to divide rapidly, while the other shows a tendency to grow, dividing very seldom. The former, he believes, have a male, the latter a female, potentiality. The relative proportion of anabolic and katabolic cells determines whether the larva becomes ♂ or ♀. The lamprey, like the frog, thus carries the potentiality of both sexes, and its sex is not irrevocably fixed at the time of fertilisation. Other cases of apparent sex-reversal are considered in a later section of this chapter.

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[1] Cuénot, "Sur la Détermination du Sexe chez les Animaux," *Bull. Sci. de France et Belg.*, vol. xxxii., 1899.

[2] Morgan, *Experimental Zoology*, New York, 1907.

[3] King, "Food as a Factor in the Determination of Sex in Amphibians," *Biol. Bull.*, vol. xvi., 1909. "Temperature as a Factor, etc.," *Biol. Bull.*, vol. xviii., 1910. See below, pp. 668-669 and pp. 692-693.

[4] Witschi, "Der Hermaphrodismus der Frosches und seine Bedeutung fur das Geschlechtsproblem und die Lehre von der inneren Sekretion der Keimdrüsen," *Arch. f. Entwick.*, vol. xlix., 1921, also short paper in *Am. Nat.*, 1921. Witschi describes the frog as having an indifferent gland which might develop either into an ovary or into a testis, but the latter is rare. Far more individuals develop first ovaries which are later transformed into testes in the larva. Oviducts grow in association with ovaries up to the time of transformation. Lateral hermaphrodites are not uncommon. (See footnote, p. 700.)

[5] Crew, "Sex-Reversal in Frogs and Toads: A Review of the Recorded Cases of Abnormality of the Reproductive System and an Account of a Breeding Experiment," *Jour. of Gen.*, vol. xi., 1921.

The experiments of Treat[2] and other observers who attempted to show that the sex of caterpillars could be determined artificially by regulating the supply of food should perhaps be disregarded, as it has since been shown that the sex in those animals is probably established at the time of hatching. Furthermore, experiments by Briggs[3] and other investigators have failed to support the hypothesis that the proportion of the sexes can be altered by modifying the diet, while Kellogg[4] has shown that with the silkworm moth, sex is determined as early as immediately after the first larval moulting, this conclusion being based on an examination of the rudimentary reproductive glands.

According to Cuénot,[5] the essential organs of reproduction in the maggots of flies are not differentiated into ovaries or testicles until a late period of larval development. It seemed possible, therefore, that in these animals the sex could be modified by the conditions of nutriment or other external factors. Cuénot found, however, that the proportion of the sexes was not materially affected by the supply of nourishment, although the maggots were fed upon different kinds of food, some being given brain, suet, and a little meat, some a large supply of putrefying flesh, while others were relatively starved.

Among bees and other hymenopterous insects the nutriment appears to be the main factor determining the difference between the two kinds of females (workers and queens). A worker larva can be made to develop into a queen by supplying "royal food," that is, food which is given to young queens. In the worker the female generative organs never fully develop, but royal diet stimulates these organs to grow so that the larvæ become queens. A partially developed worker may be made partially fertile by supplying it with some of the jelly obtained from a royal cell. The following table shows the relative composition of the solid food given to workers and queens[1]:—

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[1] Okkelberg, "The Early History of the Germ Cells in the Brook Lamprey, *Entosphenus Wilderi* (Gage), up to and including the period of Sex-differentiation," *Jour. of Morph.*, vol. xxxv., 1921.

[2] Treat, "Controlling Sex in Butterflies," *American Naturalist*, vol. vii., 1873.

[3] Briggs, "Notes on the Influence of Food in Determining the Sexes of Insects," *Trans. Entom. Soc.*, London, vol. i., 1871.

[4] Kellogg, "Notes on Insect Bionomics," *Jour. of Exp. Zool.*, vol. i., 1904.

[5] Cuénot, *loc. cit.*

Solid Food.	Workers.	Queens.
Nitrogenous - - -	51·21	45·14
Fatty - - - -	6·84	13·55
Glucose - - -	27·65	20·39

This table shows that the quantity of fatty material supplied to the developing queens is very nearly double that given to the workers.

There is no evidence that drone larvæ can be converted into females by a supply of royal or other food, so that the case of bees can scarcely be regarded as affording a real instance of sex being determined by conditions of nutrition, since workers are true females whose reproductive organs and other sexual characteristics have failed to develop owing to an insufficiency of stimulating food.

The case of white ants or termites is probably comparable, though considerably more complicated, since the different kinds of sexual individuals are more numerous. The young may develop into workers, soldiers, or royal substitutes, and the latter may be further transformed into fully fertile or "royal" individuals, while both sexes (*i.e.* males and females) are represented in each of these forms. Grassi's observations[2] point strongly to the conclusion that these different kinds of individuals are developed from similar eggs under different conditions of nutrition which is supplied to the young by the older members of the community; but here again there is no evidence that males can be converted into females or females into males.

Rolph[3] has described a series of observations on the production of males and females in *Nematus ventricosus*, a species of sawfly. These observations show that the percentage of females in broods of larvæ reared from fertilised ova steadily increased from June to August and then proceeded to diminish. "We may conclude without scruple, that the production of females from fertilised ova increases with the temperature and with the food supply (Assimilationsleistung), and decreases as these diminish."[1] Certain further experiments with unfertilised ova of the same species seem to show that "the more abundant the metabolism (Stoffwechsel) and the nutrition, the greater the tendency to the production of females." In the normal condition males only were produced as a result of parthenogenetic development, but the superior nutrition is believed to have led to the production of females.

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[1] Geddes and Thomson, *loc. cit.*

[2] Grassi and Sandias, "The Condition and Development of the Society of Termites," *Quar. Jour. Micr. Science*, vols. xxxix. and xl., 1896-97.

[3] Rolph, *Biologische Probleme*, Leipzig, 1884.

The fact that in certain Crustacea a condition of hermaphroditism can be induced by an external cause acting on a sexually differentiated individual is discussed below in dealing with latent characters, and further observations of a comparable character and relating to other animals are also considered.

(2) THEORIES WHICH ASSUME THAT SEX-DETERMINATION TAKES PLACE AT THE TIME OF FERTILISATION OR PREVIOUSLY TO FERTILISATION.

Effect of Fertilisation.—While it seems certain that queen and worker bees are developed from fertilised eggs under different conditions of nutrition, the conclusion is now fairly established that drones or male bees arise parthenogenetically from unfertilised eggs. If this view is correct, it clearly follows that in bees the differentiation into female and male individuals is brought about by the occurrence or non-occurrence of fertilisation. This theory of sex-determination in the bee was first formulated by Dzierzon,[2] and has since been accepted by Weismann[3] and many other biologists, although some writers, such as Beard,[4] deny the conclusion that fertilisation is capable of exercising any such influence.

In support of his contention Beard quotes an observation by Weismann and Petrunkewitsch, showing that a drone egg may occasionally undergo fertilisation. He also refers to the results obtained by "bastardising" hives of bees through the introduction of Italian queens into colonies of German workers and drones, or of German queens into Italian swarms.[5] In such a bastard hive Dzierzon found a drone which appeared to be a cross between a German and an Italian bee, and which consequently afforded evidence of a drone egg having been fertilised. This result led Dzierzon temporarily to doubt the truth of his hypothesis, but he subsequently accepted the interpretation of von Siebold, who suggested that the queen which had given rise to the apparently bastard drone was herself of impure descent, and that in reality the egg had not been fertilised. A further exceptional case has been recorded by Perez,[1] who found that a considerable number of male bees produced by an Italian queen which had been fertilised by a French drone appeared to be of mixed blood. This result, which is admittedly unusual, has been explained by Sanson[2] as due to "reversion," and Morgan has pointed out that the hybrid drones may conceivably have arisen from hybrid workers which sometimes lay eggs, and further that male bees are often very variable in their characters. Either of these explanations would appear to be possible.

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[1] Translated by Geddes and Thomson.

[2] Dzierzon, "Über die Befruchtung der Königin," *Eichstadt Bienen-Zeitung*, vol. i., 1845.

[3] Weismann, "Ueber die Parthenogenese der Bienen," *Anat. Anz.*, vol. v., 1900.

[4] Beard, "The Determination of Sex in Animal Development," *Zool. Jahrb.*, vol. xvi., 1902.

[5] Von Siebold, *Wahre Parthenogenesis bei Schmetterlingen und Bienen*, Leipzig, 1856.

Moreover, the later observations of Petrunkewitsch,[3] showing that sperm nuclei are not found in drone eggs whereas they are commonly met with in worker eggs, supply an important confirmation of Dzierzon's hypothesis.

Attempts to extend this hypothesis to other hymenopterous insects have not been so satisfactory, though it seems, as a general rule, to hold good for ants. There are instances on record, however, in which worker ants have developed from parthenogenetic ova, and other exceptional cases have been stated to occur.[4]

Among the Tenthredinidæ or sawflies also the unfertilised eggs commonly develop into males, but this is by no means invariable. Thus in some forms fertile parthenogenetic females only have been known to arise for many generations in succession without the appearance of males.[5]

In the parthenogenetic Rotifer, *Hydatina*, Maupas[6] has adduced strong evidence that if the parthenogenetic male eggs are fertilised they are thereby converted into "winter" eggs which give rise solely to females. If this is so (and Maupas's conclusions are now generally accepted), it is a clear instance of fertilisation altering the sex of the individual. It is stated, however, that impregnation has no effect unless it is performed during the first few hours after hatching. Moreover, parthenogenetic female eggs are also produced.

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[1] Perez, "Mémoire sur la Ponte de l'Abeille reine et la Théorie de Dzierzon," *Annales des Sciences Nat.*, vol. v., 1878.

[2] Sanson, "Note sur la Parthénogènése chez les Abeilles," *Annales des Sciences Nat.*, vol. v., 1878.

[3] Petrunkewitsch, "Die Richtungskörper und ihr Schicksal im befruchteten und unbefruchteten Bienenei," *Zool. Jahrb.*, vol. xiv., 1901. "Das Schicksal der Richtungskörper im Drohnenei," *Zool. Jahrb.*, vol. xvii., 1902.

[4] Wheeler, "The Origin of Female and Worker Ants from the Eggs of Parthenogenetic Workers," *Science*, vol. xviii., 1903.

[5] Doncaster, "On the Maturation of the Unfertilised Egg and the Fate of the Polar Bodies in the *Tenthredinidæ*," *Quar. Jour. Micr. Science*, vol. xlix., 1906.

[6] Maupas, "Sur la Multiplication et la Fécondation de l'Hydatina senta," *C. R. de l'Acad. des Sci.*, vol. cxi., 1890. "Sur la Fécondation de l'Hydatina senta," *C. R. de l'Acad. des Sci.*, vol. cxi., 1890. "Sur la Déterminisme de la Sexualité chez Hydatina senta," *C. R. de l'Acad. des Sci.*, vol. cxiii., 1891. Lenssen, Contribution a l'Étude du Développement, etc., chez l'Hydatina, *La Cellule*, vol. xv., 1898.

In recent years a large number of further experiments have been made with this rotifer by Whitney[1] and also by Shull,[2] in an attempt to determine the conditions controlling sex-production. Whitney has been able to change a pedigree stock of *Hydatina senta* from a parthenogenetic female-producing variety, kept on *Polytoma*, to a male-producing sexual stock by altering the diet to *Chlamydomonas.* This change, as Doncaster has pointed out, however, is not a real sex change but rather a change from one mode of reproduction to another. The converse change could also be brought about.

Certain writers have adopted the view that sex in animals generally is regulated by the time at which fertilisation takes place, that is to say, by the condition of the germ-cells. Thus, Thury[3] and subsequently Düsing[4] expressed the opinion that an egg which is fertilised shortly after ovulation usually develops into a female, and that an older egg tends to produce a male. Thury claimed that he could regulate the sexes in cattle by allowing coitus only at the beginning or at the end of the œstrous periods, an early coitus being supposed to result in the birth of a female, and a late coitus in the production of a male.

Pearl and Parshley,[5] who have dealt with the matter statistically in the cattle at the Maine Experiment Station, have found that as the time of copulation approaches the end of the œstrous period, there is a progressive increase in the proportion of male calves born. They have thus confirmed Thury and Düsing.

Pearl and Salaman[6] have also investigated the question in man, but found the evidence unsatisfactory.

Richard Hertwig,[7] and later Kuschakewitsch, have carried out a series of experiments on frogs, and these also show that over-ripeness of the ova was associated with a preponderance of males, and in some cases even to the total exclusion of females. Kuschakewitsch[1] showed that the results could not have been due to differential mortality or differential fertilisation, and that seemingly, therefore, the metabolic condition of the gametes must have been the cause of the unusual proportions. King[2] also has shown that the sex-ratio in toads can be affected by the metabolic condition of the eggs, as by treating the eggs so as to reduce their water content more females were produced, and by causing the eggs to absorb water more males were produced.

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[1] Whitney, "The Control of Sex by Food in Five Species of Rotifers," *Jour. of Exp. Zool.*, vol. xx., 1916.

[2] Shull, "Relative Effectiveness of Food, Oxygen, and other Substances in Causing or Preventing Male Production in *Hydatina*," *Jour. of Exp. Zool.*, vol. xxvi., 1918, and long series of papers on the same subject in the same journal previous to this date. (See also below, p. 670.)

[3] Thury, *Ueber das Gesetz der Erzeugung der Geschlechter*, Leipzig, 1863.

[4] Düsing, "Die Regulierung des Geschlechtsverhältnisses bei der Vermehrung, etc.," *Jenaische Zeitsch.*, vol. xvii., 1884.

[5] Pearl and Parshley, "Data on Sex-determination in Cattle," *Biol. Bull.*, vol. xxiv., 1913.

[6] Pearl and Salaman, "The Relative Time of the Fertilisation of the Ovum and the Sex-ratio amongst Jews," *Amer. Anthropologist*, vol. xv., 1913.

[7] Hertwig, "Ueber das Problem des sexuellen Differenzieurung," "Weitere Untersuchungen, etc.," *Verhandl. Deutsch. Zool. Ges.*, vols. xv., xvi., and xvii., 1905-06-07.

Influence of Nutrition and Environment.—Schenk[3] also has elaborated a highly speculative theory which supposes sex to be determined by the relative degree of "ripeness" or "unripeness" of the ovum; but the term "unripeness" is here used to imply a condition consequent upon incompleteness of nutrition, while "ripeness" is held to result from a more favourable state of nutrition. "Ripe" ova are supposed to develop into males, and "unripe" ones into females. The presence of sugar in the urine is evidence of an incomplete metabolism, and hence is regarded by Schenk as implying a condition likely to result in the birth of females. By supplying women with a highly nitrogenous diet, which prevented the elimination of sugar in the urine and made the metabolism more complete, Schenk claimed that he could ripen the ova, and so increase the chances of male offspring.

Cuénot[4] has described some experiments upon rats, in which some were fed mainly upon bread, and others were given an abundant supply of different kinds of food. Schultze[5] did some similar experiments upon mice, but in neither case was there any evidence of a preponderance of the sex among the young of the better nourished individuals. (For Seiler's work on *Talaporia*, see p. 671.)

It has long been known that parthenogenesis is the normal method of reproduction among plant-lice or Aphides during the months of summer, successive generations of individuals arising in this way, but that with the approach of autumn males make their appearance, and reproduction then becomes sexual. If, however, the Aphides be kept in an environment of artificial warmth, and at the same time are supplied with abundant food, the succession of parthenogenetic females may be caused to continue for years without the appearance of the sexual form. It is to be noted that the sexual and parthenogenetic females are not identical, and also that the same female may give rise to parthenogenetic and sexual offspring, or to males and females, or to only one sex. Moreover, Stevens has shown that male and female embryos may be produced practically simultaneously by the same individual. It is maintained, therefore, by this writer that "the changes in sex usually attributed to changes in external conditions are really a change from the parthenogenetic to the sexual mode of reproduction. The life cycle is often very complicated, and in some species of Aphides there is evidence that the environment (*e.g.* the trees on which they live) rather than the temperature is responsible for the development of the sexual forms.[1]

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[1] Kuschakewitsch, *Die Entwicklungsgeschichte der Keimdrüsen, etc.*, Festschr. R. Hertwig, vol. ii., 1910.

[2] King, "Studies on Sex-Determination in Amphibians," IV., *Biol. Bull.*, vol. xx., 1911. The other papers in this series should be consulted.

[3] Schenk, *The Determination of Sex*, English Translation, London, 1898.

[4] Cuénot, *loc. cit.*

[5] Schultze, "Zur Frage von den geschlechts-bildenden Ursachen," *Arch. f. Mikr. Anat.*, vol. lxiii., 1903.

Many of the lower Crustacea undergo a somewhat similar alternation of generations. For example, the water-flea (*Daphnia*), after reproducing parthenogenetically during the summer time, deposits eggs which give rise to sexual forms at the commencement of autumn, and the female after impregnation lays the winter eggs from which the new brood arises. This result is generally supposed to be brought about by the conditions of temperature or nutrition. But Weismann,[2] as a consequence of numerous experiments and observations, has cast doubts upon this view, believing rather that the animal has been so constituted by natural selection that it tends spontaneously to reproduce sexually in the appropriate season, and that it does so to a large degree irrespectively of the actually existing conditions. More recently Issakowitsch[3] has carried out an investigation upon another daphnid, *Simocephalus*, from which he has been able to show that differences in temperature may determine the mode of reproduction, but that this result is effected indirectly by the change of temperature altering the conditions of nutrition. Unfavourable conditions tend to the production of sexual forms, and favourable ones to the parthenogenetic method of generation. The same individual female may give rise either to sexual or parthenogenetic offspring, the conditions which exist in the ovary appearing to determine what kind of egg will develop.

In the Rotifer *Hydatina senta* there are at least two kinds of females, which are distinguished by the kinds of eggs that they lay: (1) thelytokous females, which produce other females parthenogenetically, and (2) arrenotokous females, which produce males parthenogenetically. The second kind of female may also produce fertilised eggs. Furthermore, the thelytokous females may give rise either to arrenotokous females or to more thelytokous females, and the proportion of arrenotokous females so produced is liable to considerable variation. Maupas[1] has sought to connect this variation with differences in temperature, and Nussbaum[2] with differences in nutrition, but neither conclusion has been satisfactorily established. The question has been reinvestigated by Punnett,[3] who has carried out a number of further experiments. In one of these a strain which had hitherto appeared to be purely thelytokous was subjected to considerable fluctuations of temperature. The rate of reproduction was much retarded, but in the subsequent generations which were produced no arrenotokous females could be found. Starvation experiments were undertaken, and in these also thelytokous females which had hitherto "bred true" continued to do so. Punnett concludes that neither temperature nor nutrition has any influence in determining the production of arrenotokous females. On the contrary, it is the property of certain females to produce arrenotokous females in a definite ratio, and the property of others to produce none.

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[1] Balbiani, "Le Phylloxera du Chêne et le Phylloxera de la Vigne, etc.," *Mém. à l'Acad. des Sci.*, vol. xxviii., 1884. Stevens, "Studies on the Germ Cells of Aphides," Carnegie Institution (Washington) Publications, 1906.

[2] Weismann, "Beiträge zur Naturgeschichte den Daphniden," *Zeitsch. f. wiss. Zoologie*, vols. xxvii., xxviii., xxx., and xxxiii., 1876-79.

[3] Issakowitsch, "Geschlechtsbestimmende Ursachen bei den Daphiden," *Biol. Centralbl.*, vol. xxv., 1905.

Theories which assume that the Gametes are themselves Sexual.—Many biologists have entertained the conception that the gametes are themselves sexual, and a number of facts have been adduced which give very strong support to this idea. Some of these have already been mentioned, but probably the strongest evidence in favour of this generalisation is that relating to the existence of special sex chromosomes contained in the ova or spermatozoa.

Seiler[4] has shown in *Talaeporia tubulosa* that the direction in which the maturation spindle turns during division determines whether the sex chromosome remains in the egg or passes out in the polar body.[5] If it remains in, then the egg is male determined, and if it passes out, female. The interest of his observations lies in the evidence he has adduced that this condition can be experimentally controlled by heat or cold. If the eggs are kept in the cold, 3° to 5° C., a higher proportion of females appear (ratio 155 ♀ to 100 ♂), the sex chromosome[1] passing into the polar body; at a temperature of 35° to 37° C., however, fewer females appear (ratio 62 ♀ to 100 ♂). This work has been well reviewed by Goldschmidt.[2]

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[1] Maupas, *loc. cit.* See also Lenssen, *loc. cit.*

[2] Nussbaum, "Die Entstehung des Geschlechts bei *Hydatina senta*," *Arch. f. Mikr. Anat.*, vol. xlix., 1897.

[3] Punnett, "Sex-determination in *Hydatina*," *Proc. Roy. Soc.*, B., vol. lxxviii., 1906.

[4] Seiler (J.), "Das Verhalten der Geschlechtschromosomen bei Lepidopteren," *Arch. f. Zellforsch.*, vol. xiii., 1914. "Geschlechtschromosomenuntersuchungen an Psychiden," *Zeitschr. f. ind. Abst. u. Vererbungslehre*, vol. xviii., 1917.

[5] In this respect Morgan's observation on *Phylloxera* (*Jour. of Exp. Zool.*, vol. vii., 1909) should be recalled. It would seem that here the behaviour of the sex chromosomes is controlled by some factor, for it can be seen in certain oögonial divisions that one daughter cell (on account of its small size) has already had its sex determined before the chromosomes have commenced to draw apart and move into their respective daughter cells, so that the chromosome complex of the daughter cells can hardly be claimed as the sex-determining factor in this instance, but more properly as a sex resultant.

It has been known for a long time that two kinds of sperm exist in the snail *Paludina*, a hair-like form and a worm-like form, but it is commonly believed that only the former is functional. Dimorphic spermatozoa have also been discovered in various other animals, but the differences between the two kinds vary greatly.[3]

Henking[4] made the discovery that in the bug, *Pyrrhocoris*, half of the spermatozoa differ from the other half in possessing an additional chromosome. M'Clung[5] was the first to suggest that the difference between the two sorts of spermatozoa in this insect was connected with sex-determination, and that those which contained the accessory chromosome produced males, and that those without it produced females. The last assumption has, however, proved to be incorrect, since Wilson[6] found that in this and other forms the female and not the male contains an additional chromosome in its somatic cells. It is almost certain also that the ova have one more chromosome than one half of the sperms have, and the same number as that possessed by the sperms which contain the additional chromosome. Consequently the latter are supposed to produce females, and the former males.

For example, in *Anasa tristis* the somatic cells of the male contain twenty-one chromosomes, whereas those of the female contain twenty-two. Half of the spermatozoa are supposed to contain eleven chromosomes, the other half having only ten. The ova are believed to all resemble one another in containing eleven chromosomes. It is concluded, therefore, that the spermatozoa possessing the smaller number give rise to males, while those with eleven chromosomes produce females.[7]

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[1] See below, p. 673.

[2] Goldschmidt (R.), *Mechanismus und Physiologie der Geschlechtsbestimmung*, Berlin, 1920.

[3] A list of species in which dimorphic forms of spermatozoa have been recorded (down to 1902) is given by Beard, *loc. cit.*

[4] Henking, "Untersuchungen ueber die ersten Entwicklungsvorgänge in den Eien der Insekten," *Zeitsch. f. wiss. Zool.*, vol. xlix., 1890, and vol. li., 1891.

[5] M'Clung, "The Accessory Chromosome Sex Determinant," *Biol. Bull.*, vol. iii., 1902.

[6] Wilson (E. B.), "Studies on Chromosomes," *Jour. of Exp. Zool.*, vols. ii. and iii., 1905-06; vol. vi., 1909. "Note on the Chromosome Groups of *Metapodius* and *Banasa*," *Biol. Bull.*, vol. xii., 1907. "The Supernumerary Chromosomes of Hemiptera," *Science*, vol. xxvi., 1907. See also Stevens, "Studies in Spermatogenesis," Part I., 1905, and Part II., 1906, Carnegie Institution (Washington) Publications. In these papers dimorphic spermatozoa (one kind containing one smaller chromosome or lacking one chromosome) are described for various species of Orthoptera, Coleoptera, Hemiptera, and Lepidoptera.

[7] Foote and Strobell ("A Study of Chromosomes in the Spermatogenesis of *Anasa tristis*," *Amer. Jour. of Anat.*, vol. vii., 1907), as a result of an investiga-

Payne[1] has recently shown that in *Galgulus oculatus* there are two sorts of spermatozoa possessing respectively sixteen and nineteen chromosomes, whereas the eggs are uniform in containing nineteen chromosomes. Furthermore, the females are believed to have three more chromosomes than the males (*i.e.* thirty-eight as compared with thirty-five).

In another insect, *Lygæus bicrucis*, the male differs from the female, not in having fewer chromosomes, but in the possession of a pair of different sized chromosomes. The body-cells in the male have twelve ordinary chromosomes and two sex chromosomes which behave differently from the others. One of the sex chromosomes is larger than the other, and has been called the X chromosome, the second or smaller one being termed the Y chromosome.

After synapsis, or the pairing of the chromosomes preparatory to spermatogenesis, there are six double chromosomes, and the two sex chromosomes, X and Y, which remain separated. At the first maturation division all the chromosomes divide, the two resulting cells each having eight chromosomes, including the X and Y. At the second division, however, although all the other chromosomes divide, the X and Y chromosomes do not divide, but each passes into a separate product of division, that is, into a separate spermatozoön. Each spermatozoön, therefore, contains six ordinary chromosomes and either an X or a Y chromosome. In the female body-cells there are twelve ordinary chromosomes and two sex chromosomes which are similar, X and X. Preparatory to oögenesis there are seven double chromosomes, the X's uniting together just as the other chromosomes unite in pairs. The polar bodies are formed, and reduction occurs in the usual way, each egg containing six ordinary chromosomes and one X chromosome. The ova, therefore, are all similar, but those fertilised by spermatozoa with X chromosomes become females, and those fertilised by Y-bearing spermatozoa become males.[2]

The mode of sex inheritance displayed by *Lygæus* is believed to be characteristic of the very large class of organisms in which the males are heterozygous as regards sex, and the females homozygous.[3]

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tion with smear preparations instead of sections, find no evidence of a persisting accessory chromosome in *Anasa tristis*, and believe that the body described as such by Wilson is a plasmosome and not a chromosome.

[1] Payne, "On the Sexual Differences in the Chromosome Groups in *Galgulus oculatus*," *Biol. Bull.*, vol. xiv., 1908. Correns also has shown that in some plants there are two classes of male germ-cells, and that these are produced in equal numbers (*Die Bestimmung und Vererbung des Geschlechtes nach neuen Versuchen mit höheren Pflanzen*, Berlin, 1907).

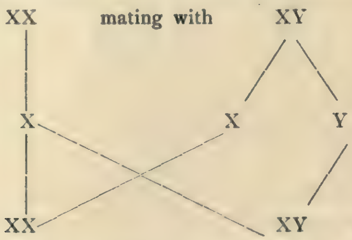
[2] Morgan, *Heredity and Sex*, New York, 1913.

[3] The term heterozygote has been given by Bateson to offspring resulting from the union of dissimilar gametes. Such organisms, according to the Mendelian theory, produce more than one sort of gamete (see p. 200). Homozygotes are formed by the union of similar gametes, and produce gametes

Essentially the same mode of inheritance occurs in those insects referred to above in which the male possesses a smaller number of chromosomes than the female, but in which the presence and peculiar nature of the sex chromosomes was not at first recognised.

As regards the Y chromosome (using this term for the smaller member of the pair in the male), it may be said that in some organisms it is as large as the X chromosome, which is its mate; in others it is smaller; while in others again it has disappeared completely.

The mode of sex inheritance just described (called by Morgan the XY type) is generalised in the following scheme:—



The case of the bee, referred to above, in which females are produced by fertilised eggs and males from unfertilised ones, belongs almost certainly to this type of sex-inheritance, both functional spermatozoa and ova containing one X chromosome. The fertilised egg and female will then contain two X chromosomes; the unfertilised egg, containing only one X chromosome, becoming a male.[1]

Bridges'[2] work, however, has shown that in *Drosophila*, among the offspring of triploid females, there are frequently a number of individuals which are neither male nor female, but are sex intermediates, being a mixture of both male and female characters. These individuals Bridges has proved, both genetically and cytologically, possess 2X chromosomes plus three sets of autosomes (or ordinary chromosomes). Thus the old formula that "2X equals female" is seen to be inadequate, for here we have 2X chromosomes, yet they are not females. It would seem that they have

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of one kind. Thus, homozygotes, as regards sex, are believed to produce gametes bearing one sex character only (either male or female); whereas heterozygotes, as regards sex, are supposed to give rise to both male-bearing and female-bearing gametes.

[1] It has been shown that the parthenogenetic gall-flies and phylloxerans may also be brought into line with animals showing the typical XY mode of sex-inheritance. Thus Morgan found that in *Phylloxera*, in which all the fertilised ova become females, the "male" spermatozoa are rudimentary.

[2] Bridges, "The Origin of Variation in Sexual and Sex-limited Characters," *Amer. Nat.*, vol. lvi., 1922.

been shifted out of the female class by the presence of an extra set of autosomes, and thus the autosomes are proved to play a positive rôle in sex-production.

Again, Blakeslee[1] finds in the jimson weed, *Datura*, many mutations with a $2n$, $3n$, or even $4n$ number of chromosomes. As long, however, as they possess a balanced chromosome number, these mutants are all remarkably stable and healthy, while all those containing an unbalanced chromosome complex, such as a $2n+1$ condition, are very unstable, and frequently undersized and often unhealthy in appearance. Thus while the $2n$ plant will be large and vigorous in appearance, the $2n+1$ individual will be half its size and very unhealthy. The presence then of an extra chromosome is capable of affecting the action of all the others. He comes to the conclusion that a species on these grounds must be the result of a whole series of more or less conflicting forces contained in the individual chromosomes acting as a whole, and not the result of any individual chromosome or number of chromosomes acting alone. This conclusion accords with Bridges' work just mentioned, and gives us a totally new conception of the action of the chromosome in heredity.

The experimental study of the transmission of sex-linked characters is in general accordance with the cytological evidence as to sex-inheritance, an outline of which has been given above Sex-linked characters are those which while ordinarily restricted to one sex, may occasionally pass over to the other. Their inheritance has been studied very fully by Morgan, in the fruit-fly, *Drosophila ampelophila*, in which as many as fifty sex-linked characters have been identified. In transmission they are supposed to be located in the X chromosome.

Drosophila usually has red eyes, but Morgan found some males with white eyes. When these latter were mated with red-eyed females, the offspring had red eyes. The heterozygous red-eyed flies when mated together gave rise to 2000 red-eyed females, 1000 red-eyed males, and 800 white-eyed males. White-eyed males with heterozygous red-eyed females gave rise to both red-eyed and white-eyed males and females, the males and females being nearly equal in number; but the white-eyed individuals, as in the previous mating, owing to less constitutional vigour, were fewer than the red-eyed. White-eyed males and females gave rise exclusively to white-eyed offspring, but red-eyed males of whatever origin when mated with white-eyed females invariably gave rise only to red-eyed females and white-eyed males.

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[1] Blakeslee, "Variation in *Datura* due to Changes in Chromosome Number," *Amer. Nat.*, vol. lvi., 1922.

The results are represented in the following scheme, where R represents the red-eyed factor and *w* the white-eyed:—

(1) RR ♀ × *ww* ♂ gave R*w* ♂ and R*w* ♀.
(red) (white) (red) (red)
(2) R*w* ♀ × R*w* ♂ gave R*w* ♂, *ww* ♂, R*w* ♀, and RR ♀.
(red) (red) (red) (white) (red) (red)
(3) R*w* ♀ × *ww* ♂ gave R*w* ♂, *ww* ♂, R*w* ♀, and *ww* ♀.
(red) (white) (red) (white) (red) (white)
(4) *ww* ♀ × R*w* ♂ gave *ww* ♂ and R*w* ♀.
(white) (red) (white) (red)
(5) *ww* ♀ × *ww* ♂ gave *ww* ♂ and *ww* ♀.
(white) (white) (white) (white)

These results are to be explained on the assumption that the red-eyed male produces two sorts of spermatozoa, male-producing and female-producing, and that whereas the female-producing spermatozoa carry the factor for red eyes, the male-producing ones do not. This conclusion has received cytological confirmation in the discovery of Miss Stevens[1] that the male *Drosophila* has a pair of unequal chromosomes, and Morgan naturally assumes that the larger or X chromosome carries the sex-linked characters.

Doncaster had previously found in the currant moth, *Abraxas grossulariata*, a condition of things which is the precise converse of what Morgan has established for *Drosophila*. He showed that in with this insect there is a rare variety, which generally occurs only in the female sex. This variety, which is called *A. grossulariata lacticolor*, is a Mendelian recessive, so that when crossed with an ordinary *grossulariata* male, the offspring are all typical, the *lacticolor* variety disappearing. Experimental crossings yielded the following results:—

(1) Lact. ♀ × gross. ♂ gave males and females all gross.
(2) Heterozygous ♀ × heterozygous ♂ gave gross. ♂, gross. ♀, and lact. ♀.
(3) Lact. ♀ × heterozygous ♂ gave all four possible forms (gross. ♂, lact. ♂, gross. ♀, and lact. ♀), the lacticolor males being the first ever seen.
(4) Heterozygous ♀ × lact. ♂ gave gross. ♂ and lact. ♀.
(5) Lact. ♀ × lact. ♂ gave lact. ♂ and lact. ♀.
(6) Wild gross. ♀ × lact. ♂ gave gross. ♂ and lact. ♀.

It is shown, therefore, that males of the *lacticolor* variety can be produced by mating lacticolor females with heterozygous males (*i.e.* with males obtained by crossing the two original varieties, and so presumably bearing two sorts of gametes), but that the converse mating (4) results in offspring which are either grossulariata males or lacticolor females. Furthermore, whereas lacticolor females mated with wild grossulariata males (1) produce offspring which are of both sexes, but all of the grossulariata variety, the converse cross (6) yields grossulariata males and lacticolor females. It is concluded, therefore, that the wild and presumably pure grossulariata females are heterozygous for sex, femaleness being dominant and maleness a homozygous recessive character. All the females are believed to produce male-bearing and female-bearing gametes in equal numbers, whereas all the males appear to produce only one sort of spermatozoön. In confirmation of this conclusion Doncaster since discovered a pair of unequal chromosomes in the *female Abraxas*, corresponding therefore with the X and Y chromosomes of the other insects described.

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[1] Stevens, "A Study of the Germ Cells of Certain Diptera," *Jour. Exp. Zool.*, vol. v., 1908.

The results obtained by Miss Durham in her experiments on cinnamon canaries are explicable on a similar hypothesis. When a cinnamon male was mated with a green female, the female offspring were cinnamon and the males green; but when a cinnamon female was paired with a green male, all the offspring of both sexes were green.[1] Where, however, a green cock of the second generation (the F_1 generation produced by crossing) was mated with a cinnamon hen, both green and cinnamon birds of both sexes were produced; but when a green cock of the second (F_1) generation was crossed with a green hen the resulting male birds were all green, but the females were of both types. A more complex case of a like kind has been brought to light by Bateson and Punnett in their investigation on the heredity of the black pigmentation of the silky fowl in its crosses with brown Leghorns and other fowls with light shanks. Here two allelomorphic characters, in addition to the two sex determinants, are concerned, but Bateson and Punnett state that the facts point very clearly to some such solution as that indicated by Doncaster's experiments with *Abraxas*. A clearer case is that of the factor for barring in the Barred Plymouth Rock. If a barred cock is mated with an unbarred hen (Cornish Indian Game) all the chicks of both sexes are barred; if a barred hen is mated with an unbarred cock, all the males are barred and all the females unbarred.[2] Similar results have been obtained with other breeds.[3]

The mode of sex-inheritance shown by *Abraxas* and the other animals cited has been called by Morgan the WZ type. It is represented diagrammatically as follows:—

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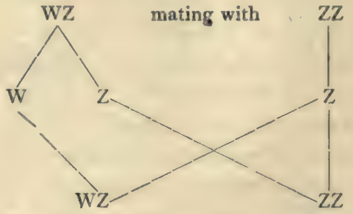
[1] Durham, *Report to the Evolution Committee of the Royal Society*, IV., London, 1908.

[2] Pearl and Surface, "On the Inheritance of the Barred Pattern in Poultry," *Arch. f. Entwick.-Mech.*, vol. xxx., 1910. The sex-linked factor for high egg-production has been already mentioned (p. 644).

[3] See Doncaster, *The Determination of Sex*, Cambridge, 1914.



The females are heterozygous for sex, and the males homozygous—that is to say, there are two sorts of ova but one sort of spermatozoön.

This type of sex-inheritance appears to be characteristic of Lepidoptera and birds, while the XY type occurs in other insects, in Myriapods and spiders, in Nematodes, and among Vertebrates in all Mammals and probably also in fishes and Amphibians.[1]

Parkes,[2] as a result of an ingenious research on numerical sex-inequality in man, has arrived at very clear conclusions in support of the view that the male is heterozygous and the female homozygous for the sex-determinant. He examined many dozens of genealogies, and of these found six to be abnormal in having a proportion of more than 1100 males to 1000 females. The total number of individuals was 1792, of which 1001 were males and 791 were females. When the female lines were separated from the male the following results were obtained:—

Male lines - -	1167 :	males, 685;	females, 482.
Female lines - -	625 :	„ 316;	„ 309.

It was thus found that the excessive male-bearing tendency was vested exclusively in the male line, which indicates that the spermatozoa carry the sex-determinant, and that the abnormal ratio is not accounted for by selective fertilisation.

It has been shown, however, that with some animals, whereas a certain chromosome constitution is undoubtedly usually correlated with a particular sex, it cannot be regarded as the efficient cause of that sex, since it may under special conditions be overridden, and the alternative sex produced (see pp. 663 and 693).

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[1] King states that only one X chromosome occurs in the male of the Amphibian, *Necturus* (*Anat. Record*, vol. vi., 1912). Among Mammals Wodsedalek has found two sorts of sperms in the horse and pig. The numbers of somatic chromosomes are: horse, ♂ 36, ♀ 38; pig, ♂ 18, ♀ 20 (*Biol. Bull.*, vols. xxv., xxvii., and xxx., 1913-14-17). In man there is some dispute about the numbers of chromosomes, but according to von Winiwarter there are forty-seven in the male and forty-eight in the female (*Arch. de Biol.*, vol. xxvii., 1912). (See p. 168.)

[2] Parkes, "Sex-Heredity, with Special Reference to Abnormal Numerical Inequality between the Sexes," *Science Progress*, vol. xv., (April) 1921.

The view that sex is determined entirely by the ova had been put forward some time previously by Beard, who stated that in the skate, *Raja batis*, there were two kinds of eggs—one large, which gave rise to females, and another small, which produced males. He pointed out that there were two sizes of eggs in *Hydatina senta*, *Phylloxera*, and *Dinophilus apatris* as well as in other animals, and that these were related to sexual differences.

It is also pointed out in support of Beard's view that according to von Ihering[1] embryos which are found in one chorion (and which are supposed, therefore, to have arisen from one ovum) in the Edentate *Praopus hybridus*, are invariably of one sex, and that "double monsters" in man are of the same sex, while Marchal[2] states that in the chalcid fly (*Ageniaspis fuscicollis*), in which a chain of embryos takes origin from a single egg, these embryos are all of one sex.

The view has also been entertained that there is a relation between the position of the ovary and the sex of the ova. Thus, according to Rumley Dawson,[3] the ova produced by the right ovary become males, and those produced by the left become females. This theory is believed to be applicable especially to man, and is based on clinical evidence and on a supposed alternation of the sexes of the eggs discharged at the ovulation periods. It clearly cannot apply to birds, in which the left ovary only is functional, and King[4] has shown experimentally that it is inapplicable to Amphibians. The theory as well as the alternative one that sex depends on the position of the testis from which the fertilising spermatozoön was derived has been negatived by Copeman[5] as a result of an experimental investigation upon rats.

Heape[6] has expressed the belief that "each ovum and spermatozoön in the generative glands contains within itself sex, which is probably determined by the laws of heredity, but that the proportion of those male and female ova and spermatozoa which are developed and set free from the generative glands may be regulated by selective action, exerted in accordance with the resultant of a variety of extraneous forces. If this be true, the proportion of living male and female ova and spermatozoa which are freed from the generative glands, and the proportion of the sexes of the offspring which result therefrom, will thus be influenced."

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[1] Von Ihering, "Ueber Generations-wechsel bei Säugethieren," *Biol. Centralbl.*, vol. vi., 1886. Newman, *The Biology of Twins*, Chicago, 1917.

[2] Marchal, "Recherches sur la Biologie et le Développement des Hymenoptères parasites," *Arch. de la Zool. Expér. et Gén.*, vol. ii., 1904.

[3] Dawson, *The Causation of Sex*, London, 1909.

[4] King, "Studies on Sex Determination in Amphibians," *Biol. Bull.*, vol. xvi., 1909.

[5] Copeman, "Sex-Determination," *Phys. Soc.*, May 1908 (unpublished). The results were eventually published in abstract in *Proc. Zool. Soc.*, 1919, which contains further suggestive information. See also Doncaster and Marshall, *Jour. of Genetics*, vol. i., 1910; and King, *Jour. of Exp. Zool.*, vol. x., 1911.

[6] Heape, "Note on the Proportion of the Sexes in Dogs," *Proc. Camb. Phil. Soc.*, vol. xiv., 1907.

Heape is of opinion, however, that just as there is evidence that adult animals are never purely male or female,[1] so it is probable that the sexual products (*i.e.* the gametes) are themselves similarly constituted. According to this view, an ovum or a spermatozoön may possess dominant male or female characters as the case may be, and recessive characters of the opposite sex. "In such cases the possibility of infinite gradations of sexual differentiation in an individual would be vastly increased, and from the point of view of heredity, such complex conditions carry with them factors of the highest importance."

Ova and spermatozoa in which the characters of one sex are dominant are referred to as being male and female, and Castle's conclusion[2] that an ovum of one sex must always be fertilised by a spermatozoön of the opposite sex is adopted, but whether the sex of the adult is determined by the ovum or by the spermatozoön is a question which is left open, as it may admit of a different answer for different species of animals, or even for different individuals. Heape says, however, that even if that be so, the sex of the ovum must be regarded as bearing a regular relation to the sex of the embryo as surely as if it conferred its own sex.

"On this assumption a female parent producing ova of one sex only will give birth to embryos of one sex, unless the male parent possesses no spermatozoa of the opposite sex wherewith to fertilise it, in which case the union will be barren. Düsing[3] claimed that the statistical results he obtained from a study of the mating of Thoroughbred horses indicated the dominant influence of the male parent on the sex of the offspring. Any sire that usually produces spermatozoa of one sex only can be fertile, as a rule, only with mares which produce ova of the other sex, and to such an extent he determines the proportion of the sexes of the offspring for which he is responsible. But where the sperm of both sexes is uniformly produced, the sire must be fertile with all mares producing ova, and as only one ovum is produced by each mare, the responsibility for the sex of the offspring then lies solely with the female parent."

The opinion is expressed that much of the evidence cited to show the dominating influence of the male parent on the offspring produced may be explained on this view: "While statistically the father might be shown to be responsible, physiologically the mother controls the governing influence."

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[1] Evidence on this point, including some of that adduced by Heape, is cited below in dealing with hermaphroditism and the latency of sexual characters.

[2] Castle, "The Heredity of Sex," *Bull. Museum Compt. Zool.*, Harvard, vol. xl., 1903.

[3] Düsing, *loc. cit.*

It is assumed that in normal cases both sexes of ova and spermatozoa are probably produced in the gonads in equal quantities, and that in those females which shed all their ova the proportion of the sexes in the offspring is, in all likelihood, determined by Mendelian laws. But it is pointed out that in many animals only a small proportion of the ova formed in the ovary ever reach maturity, the remainder undergoing degeneration and ultimately absorption (see p. 151). It is inferred, therefore, that the proportion of the sexes among the ova which survive and are discharged must depend directly upon the causes which lead to the degeneration of some ovarian ova and the continued development of others. On this view it is held that the ova are subject to the same law of natural selection as other organisms, and that in some cases the male ova are best fitted to survive, and in other cases the female ones.

Heape[1] has shown further that in the ovary of the rabbit two kinds of degeneration prevail, and that in one kind it is the follicle which first begins to undergo atretic changes, and that in the other kind it is the ovum that is earliest affected. The former condition is regarded as evidence that the available supply of nutriment is insufficient for the maintenance of all the ova in the ovary, while the latter is interpreted to mean that the ovum, for one reason or another, is unable to assimilate the nutriment provided for it. It is possible, therefore, that nutrition may in this way exercise a selective action as regards sex. In this connection it is interesting to note that, according to Issakowitsch,[2] the nutritive conditions prevailing in the ovary of the daphnid *Simocephalus* are determinative as to the kind of egg which will develop (*i.e.* whether it will be a parthenogenetic or a "winter" egg), and that the two kinds of eggs are stated to arise in different parts of the ovary. Moreover, Heape suggests that the marked difference between the death-rate of men and women during famines,[3] for example, may be reproduced among male and female ova in the ovary when that organ is subjected to conditions of a homologous kind.

Heape's general conclusions are summarised as follows:—

"(1) That through the medium of nutrition supplied to the ovary, either by the quantity or by the quality of that nutrition, either by its direct effect upon the ovarian ova or by its indirect effect, a variation in the proportion of the sexes of the ova produced, and therefore of the young born, is effected in all animals in which the ripening of the ovarian ova is subject to selective action;

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[1] Heape, "Ovulation and Degeneration of Ova in the Rabbit," *Proc. Roy. Soc.*, B., vol. lxxvi., 1905.

[2] Issakowitsch, *loc. cit.*

[3] M'Ivor, *Madras Census Reports*, 1883.

"(2) That when no selective action occurs in the ovary the proportion of the sexes of ovarian ova produced is governed by laws of heredity."

Having arrived at these conclusions, Heape next adduces evidence that certain external forces may affect the proportion of the sexes in dogs. It is shown that amongst greyhounds, conception during the period from August to November is most favourable to the production of males under the conditions of breeding at present practised, and this result is attributed to a selective action on the ova produced at this time. There is evidence also that among dachshunds and Basset hounds the seasons affect the proportions of the males and females born. The bloodhound returns seem to show that an excessive production of males is associated with in-breeding. Further, there is statistical evidence that a higher proportion of males is produced in the larger litters, that the larger dogs produce the larger litters, and consequently that the larger breeds have a racial tendency to produce an excess of dog pups. Lastly, the schedule returns strongly support the popular belief that there is a tendency to prolonged gestation when the embryo is of the male sex.

In a further paper[1] Heape discusses the apparent influence of extraneous forces on the proportion of the sexes in two aviaries of canaries, kept under different conditions. One aviary was kept at a regular temperature during the breeding season; it was comparatively well lighted, and the sun had access to it. On the other hand, the birds did not receive specially rich nutrition. The other aviary was kept in a room facing north and east, and the temperature was allowed to vary considerably during the breeding time, but the birds were always fed with a plentiful supply of rich food. In the former of the two cases nesting, hatching, and moulting took place earlier, only about half the percentage of loss was experienced, and from the nests in which all the eggs were hatched, the percentage of males produced was more than three times that which was obtained from the other aviary, in which the environmental conditions were less favourable. The results obtained in each case could not be ascribed to the particular strains of canaries, since an interchange of birds between the aviaries was not followed by any material alteration in the proportion of the sexes in the two environments. It is concluded, therefore, that the ova were subject to a selective action on which depended the proportional differences produced.

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[1] Heape, "Note on the Influence of Extraneous Forces upon the Proportion of the Sexes Produced by Canaries," *Proc. Camb. Phil. Soc.*, vol. xiv., 1907.

"As a rule in nature the climatic forces which stimulate the activity of the generative functions are also associated with a plentiful supply of food; the conditions which excite the one ensure the supply of the other. Among domesticated animals living in the open air, on the other hand, any forcing of the breeding time is brought about by special feeding. In neither case are the results obtained comparable to those we have now before us, where both the quality and the quantity of the food supplied is regulated entirely independently of the other causes which stimulate the activity of the generative system. It is to this peculiar combination I attribute the regularity of the remarkable differences shown in these aviaries."

In a still later paper[1] Heape shows that there is evidence of the influence of extraneous forces upon the proportion of the sexes produced by the white and coloured peoples of Cuba. Illegitimate unions were found to give rise to a larger proportion of females, and it is concluded that in this class of union there is an exceptionally active metabolism of the mother which favourably affects the development of those ovarian ova which give rise to female offspring.

Heape suggests further that much of the evidence that has been collected in regard to the influence of nutrition and other environmental causes upon the proportions of the sexes, although it may be disregarded from the point of view from which it was put forward (since it is commonly assumed that the conditions directly determine the sex of the embryo), may yet be well worthy of attention from the standpoint adopted by him. Some of this evidence is briefly referred to below.

(3) THEORIES WHICH LIMIT SEX-DETERMINATION TO NO PARTICULAR PERIOD OF DEVELOPMENT, OR WHICH ASSERT THAT SEX MAY BE ESTABLISHED AT DIFFERENT PERIODS.

Influence of Age of Parent.—Hofacker[2] and Sadler[3] arrived independently at the conclusion that the sex of the offspring depends on the relative ages of the parents—that when the father is the oldest more male births occur, and similarly when the mother is the oldest there tends to be a preponderance of females. This hypothesis, which is known as Hofacker and Sadler's Law, has been both confirmed and contradicted,[4] but the most recent statistical investigation[1] on the causes controlling sex in man lends no support to it. Moreover, Schultze's experimental investigation[2] on the sexes produced by mice of different ages has led likewise to a negative result.[3]

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[1] Heape, "The Proportion of the Sexes Produced by Whites and Coloured Peoples in Cuba," *Phil. Trans.*, B., vol. cc., 1909.

[2] Hofacker, *Ueber die Eigenschaften welche sich bei Menschen und Thieren auf die Nachkommen vererben*, Tübingen, 1828.

[3] Sadler, *The Law of Population*, London, 1830.

[4] Geddes and Thomson, *loc. cit.*

Copeman and Parsons,[4] however, found that does aged over six months produced more males than does under that age, but in view of the evidence in favour of male heterozygosis as regards sex among Mammals recorded above, little stress can be laid upon such observations.

Influence of Parental Vigour or Superiority. — Considerable importance has been attached by breeders and others, and notably by Starkweather,[5] to the comparative vigour or condition of the parents as a factor in sex-determination. According to Starkweather, the superior parent tends to produce the opposite sex. This theory has been accepted by Allison,[6] who believes it to be applicable to Thoroughbred horses. It is obvious, however, that in attempting to apply Starkweather's hypothesis, much depends on the signification to be attached to the term "superiority," and for this, if for no other reason, the theory is unsatisfactory. Furthermore, Schultze[7] has shown that long-continued or strained reproduction in female mice has no effect on the proportion of the sexes produced. The results of experiments on the effects of in-breeding were also indefinite or contradictory.

Influence of Nourishment.—Of the various external factors which have been supposed to have direct influence in determining sex, nourishment seems to have found more favour than any other. In some cases this factor is supposed to act upon the developing embryo or larva (see p. 662), and so to determine its sex, while in other cases it is concluded that sex is established at an earlier period.

Geddes and Thomson have elaborated the idea that favourable nutritive conditions tend towards the production of females, and unfavourable ones towards the development of males, and certain of the evidence referred to above (p. 662) has been cited by them in support of this hypothesis. The normal female metabolism is said to be relatively anabolic, while the greater activity of the male is held to indicate a preponderance of katabolic conditions. Consequently the generalisation is reached that abundant or rich nutrition (or any other favourable circumstance) tends to induce an anabolic habit, and so favours the development of females; and conversely, that deficiency of the necessary food supply (or any adverse circumstance) leads to a katabolic condition of life, and so causes the production of males. According to this idea, the organism is at first "sexually indifferent," the sex becoming established at varying periods of development in different animals according to the circumstances. Thomson has subsequently admitted that some of the evidence which was formerly adduced in support of this view has been invalidated, since in a very large number of animals sex appears to be fixed in the fertilised ovum or earlier, and consequently subsequent conditions of nutrition ordinarily play no part in determining the relative proportion of males and females. But Thomson is still disposed to lay stress on the connection between sex and metabolism, believing that the determinants for each of the sexual characteristics (both male and female) are present in all ova and in all sperms, and that their liberation or latency depends on a bias towards egg-production or sperm-production. The so-called contrasted peculiarities of the two sexes are due in certain cases "to internal physiological conditions which give the same primordium two different expressions, much less different than they seem."[1]

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[1] Newcomb, "A Statistical Inquiry into the Probability of Causes of the Production of Sex in Human Offspring," Carnegie Institution (Washington) Publications, 1904. Newcomb states that the first-born child of any mother is more likely to be a boy in the proportion of about eight to seven.

[2] Schultze, "Zur Frage von den geschlechts-bildenden Ursachen," *Arch. f. Mikr. Anat.*, vol. lxiii., 1903.

[3] This theory, and that which follows, should possibly be included among those which assume that sex is settled at fertilisation; for if sex is determined by the age of the parents, it seems to follow that no event occurring during embryonic life can alter it. This point, however, does not appear to have been raised by the authors of the theory.

[4] Copeman and Parsons, "Observations on the Sex of Mice," *Proc. Roy. Soc.*, vol. lxxiii., 1904. For other observations of a similar kind see Goldschmidt, *loc. cit.*, where full references may be found.

[5] Starkweather, *The Law of Sex*, London, 1883.

[6] Allison, *The British Thoroughbred Horse*, London, 1901.

[7] Schultze, *loc. cit.*

Riddle[2] has elaborated a theory of sex-determination which is somewhat similar to that of Geddes and Thomson; but Riddle's view is based on experimental evidence obtained from a prolonged study of sex-phenomena in doves and pigeons. This investigator interprets sexual differentiation as the expression of quantitative differences in the rate of protoplasmic activity, the more active metabolism being associated with a production of males, and the less active with females. The theory is elaborately worked out, and it is shown that much of the accumulated evidence on this question supports (*e.g.* see above, p. 668) the view that the preponderance of male or female characteristics is conditioned by the level or rate of the metabolic processes. Large size of yolk, a low percentage of water in the yolk, a high percentage of stored material and a high total of stored energy, and an exhausted physical condition or advanced age in the mother are all associated with a low level of metabolism and with the female sex.

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[1] Thomson, *Heredity*, London, 1908.

[2] Riddle, "The Determination of Sex and its Experimental Control," *Bull. Amer. Acad. Med.*, vol. xv., 1914. "Sex-control and Known Correlations in Pigeons," *Amer. Nat.*, vol. l., 1916. "A Quantitative Basis of Sex, etc.," *Science*, vol. xxxix., 1914. "The Theory of Sex, etc.," *Science*, vol. xlvi., 1917. "A Note on Social Aspects of New Data on the Biology of Sex," *Jour. National Inst. of Social Sciences*, 1915. See also Jennings, Riddle, and Castle, *Lectures on Heredity*, Washington, 1917.

The work on pigeons and doves was begun by the late Professor Whitman, and continued after his death by Riddle, who confirmed and extended Whitman's original results. They showed that with crosses the percentage of males increases with the width of the cross until sterility is reached. Since males are characterised by a more active metabolism, the results are in agreement with the commonly observed superior vigour of hybrids. By overworking the birds, that is to say, by not allowing them to nest their own eggs and forcing them to continue laying eggs in rapid succession, the first several pairs of eggs laid in the spring produced all or nearly all males, whereas the last several pairs of eggs laid in the autumn gave rise almost or quite exclusively to females, while both sexes were produced in the summer or transition period. These results are in correlation with the fact that the developmental energy is greatest early in the season, and then declines, so that Whitman found that at the extreme end of the season the eggs were unable to hatch at all.

The possibility of assortative mating and differential death-rates are fully considered and rejected. Thus hens which when crossed throw all males will, when mated to birds of their own kind, produce both sexes equally. Moreover, the eggs are of two kinds, large and small, and these in the wild pigeon are normally associated with females and males respectively, but in the crossing experiments the birds utilise "female-producing" ova for the formation of males, and vice versa, the eggs thus changing their original sexes.

Furthermore, Riddle finds grades of sexual individuals, some females being more masculine than others, and some males coming to resemble females, and if ovarian extracts are injected into the more masculine females, and extracts of testis into the more feminine ones, the sex-behaviour of the birds may be very largely reversed, but the effect is not permanent.

Lastly, the sex of the birds could not only be changed; it could also be accentuated. The hens hatched from the second clutch laid in the autumn by overworked pigeons were found to be even more pronouncedly female than normal birds, inasmuch as the right ovary which usually atrophies, in these circumstances persists.

Needless to say, Riddle rejects the chromosome theory as an explanation of how sex is determined, and in support of his contention there is other evidence, as will be shown later, that although a certain chromosome constitution, like a secondary sexual character in an adult, is usually correlated with one sex, this constitution may, under certain conditions, be overridden and the other sex develop.

Statistical Investigations on Man.—Statistics of human births have been brought forward in support of the view that the proportion of the sexes varies with the conditions of nutrition. It has been pointed out that in France the proportion of births of boys and girls is 104·5 to 100 for the upper classes (who are presumably best nourished), and 115 to 100 for the lower classes (who are more poorly fed). In the "Almanack of Gotha" the proportion recorded is 105 boys to 100 girls, while for Russian peasants this proportion is 114 to 100. Among the nobility of Sweden statistics show a proportion of 98 male to 100 female births, but that given for the Swedish clergy is 108·6 boys to 100 girls.[1] There is therefore some slight evidence that the percentage of female births is a little higher among those classes which are best nourished or subject to more favourable circumstances, but the differences are very small.

Punnett[2] has examined the statistics collected in the official census of the county of London for the year 1901, with a view to determining the relative proportions of the sexes amongst different classes of society. The following is his summary and conclusion:—

"If the population of London be divided into three portions exhibiting graduated poverty, it is found that the proportion of male to female infants produced [or rather which have survived] is lowest in the poorest portion, highest in the wealthiest portion, and intermediate in the intermediate portion. The proportion of males is highest of all in a number of births taken from 'Burke's Peerage,' where the nutrition may be supposed to be of the best. From this alternative conclusions may be drawn: that either more favourable conditions of nutrition (1) may result in a large proportion of male births [a conclusion which is contrary to that indicated in the returns mentioned above, but which nevertheless appears to be warranted at first sight], or (2) may have no effect on the proportion of the sexes, or (3) may even result in a relative preponderance of female births, but that in the last two cases the effect is masked by other factors which affect unequally the different strata of society. Such factors are shown to exist in a differential infant mortality, a differential birth-rate, and probably also in a differential marriage-age. These factors all tend to diminish the proportion of males in the poorer portions of the population, and consequently render the first of the above alternative conclusions improbable. Whether the second or third of the other possible conclusions is to be accepted must remain doubtful so long as we are not in a position to estimate the quantitative effect of the factors given above. From the necessarily rough estimate which he has been able to form, the writer's opinion is that their combined effect would not be sufficiently great to mask a preponderance of female births due to better nutrition, and consequently he is inclined to believe that in man, at any rate, the determination of sex is independent of parental nutrition. In any case its influence can be but small."

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[1] See Morgan, *loc. cit.*

[2] Punnett, "On Nutrition and Sex-Determination in Man," *Proc. Camb. Phil. Soc.*, vol. xii., 1903.

Newcomb,[1] as a result of an investigation into the statistics of multiple births, has come to the conclusion that sex is established at different periods of development in different cases. He shows that there is a tendency among human offspring for twins to be of the same sex, a fact which he regards as supplying a "practically conclusive negation of the theory of completely determined sex in the original germs." His conclusion appears to be that sex is established by "accidental causes," the nature of which is at present unknown, and that in the case of twins the sex-determining factors act similarly on both children, and so tend towards a uniformity of sex. But he omits to mention the probability that some twin embryos arise from a single ovum, a fact which would account for their sexual identity on the assumption that sex is already determined in the germ-cell.

Hermaphroditism and Sexual Latency

Organisms which combine within themselves the essential characters of both sexes are said to be hermaphrodite. True hermaphrodites produce both ova and spermatozoa, but there are all gradations between true and partial hermaphroditism (in which the essential organs of reproduction are not involved), and between the latter and the completely unisexual condition, in which the characters of the other sex are either latent or absent altogether.

Complete hermaphroditism is the normal state in many groups of invertebrate animals (many sponges, cœlenterates, and worms, and some molluscs and crustaceans). In some forms the male and female sexual elements do not exist contemporaneously, but are called forth separately by different environmental conditions or are associated with particular phases in the reproductive cycle (see Chapter I.). In such cases the fact that the animal is hermaphrodite is liable to be obscured.

Among vertebrate animals true hermaphroditism is rare, though its casual occurrence has been recorded even in Mammalia, and is said to be comparatively frequent in certain species of Amphibia.[1]

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[1] Newcomb, *loc. cit.*

According to Castle[2] the true hermaphrodite is a sex mosaic, the alternative sexual characters existing side by side without dominance of either, and passing (without segregation) into the gametes. Diœcious individuals are supposed to result ordinarily from a union of gametes in which one sex is dominant and the other recessive, so that no one individual is purely either male or female. The occurrence of partial hermaphroditism may be held to be an expression of an incomplete dominance of the characters of one sex.

Partial hermaphroditism is usually said to occur when only one kind of gonad is developed (either testis or ovary) in conjunction with accessory generative organs characteristic of both sexes. Such cases are by no means uncommon even among the higher animals. The so-called "Free-Martins" among cattle have been held to be examples of incomplete hermaphroditism.[3]

Among animals which are usually regarded as purely diœcious there are many instances of vestigial or even of functional sexual organs characteristic of one sex being present normally in individuals of the opposite sex. The mammary glands and teats of the male mammal and the clitoris of the female are examples of such organs. A more striking case is that of the pipe-fish (*Siphostoma floridæ*), in which the male possesses a marsupium which acts functionally as a placenta.[1]

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[1] See Geddes and Thomson, *loc. cit.* Curtis, "Studies on the Physiology of Reproduction in the Domestic Fowl" (*Biol. Bull.*, vol. xvii., 1909). Pearl and Surface have described a case of an hermaphrodite fowl which had a testis on one side and an ovary on the other. The accessory organs were likewise unilaterally arranged. Externally it was an antero-posterior gynandromorph, having male characters in front but female body characters. *Cf.* Weber's chaffinch (p. 337) and Poll's bullfinch, which were lateral gynandromorphs. Such gynandromorphs are not uncommon among some insects (*Hymenoptera*). See also Shattock and Seligmann's papers quoted on p. 341, and Bateson and Thomas, "Note on a Pheasant showing Abnormal Sex Characters," *Jour. of Genetics*, vol. vi., 1917. For an account of the question of hermaphroditism in man, with a discussion of the evidence, see von Neugebaur, *Hermaphroditismus beim Menschen*, Leipzig, 1908, and Gudernatsch, "Hermaphroditismus Verus in Man," *Amer. Jour. of Anat.*, vol. xi., 1911. The latter author states that there is no clear case of true hermaphroditism in man or any mammal.

[2] Castle, *loc. cit.*

[3] Lillie's interpretation of the Free-Martin is referred to below (p. 695). According to Berry Hart, however, the Free-Martin is in reality a sterile bull which is co-twin of a normal fertile bull ("The Structure of the Reproductive Organs of the Free-Martin, with a Theory of the Significance of the Abnormality," *Proc. Roy. Soc. Edin.*, vol. xxx., 1910). The Free-Martin has also been regarded as a sterile cow born co-twin with a potent bull. In most cases a vagina and rudimentary uterus have been described, but vesiculæ seminales and other male organs are also stated commonly to occur. Berry Hart bases his explanation of the occurrence of Free-Martins upon his theory of sex (*Mendelian Action on Differentiated Sex*, Edinburgh, 1909). According to this theory, sex is determined by a "sex-gamete" which may be either male or female. There are also male and female "non-sex gametes," which unite with the "sex-gametes" but are non-potent in determining sex. A female sex-gamete uniting with a male non-sex gamete gives rise to a female zygote, and conversely. Moreover, according to Hart, a Free-Martin with a potent bull twin is the result of a division of a male zygote, so that the somatic determinants are equally divided, but the gametic determinants unequally divided, the potent going to the one twin, the potent bull, and the non-potent to the Free-Martin. It has been shown, however, by Lillie that the twins arise from two separate ova.

In the great crested grebe the positions assumed during pairing by the two sexes are interchangeable, for the male may adopt the passive attitude and the female the active one.[2] Reversal of pairing positions has also been described in moor hens and in tame pigeons. Here we have an instance of the reversal of an instinct.

Weininger[3] has elaborated the idea that just as there may be an "Idioplasm" that is the bearer of the specific characters, whether morphological, physiological, or psychological, and exists in all the cells of a multicellular animal, so also there may be two sexual modes in which this idioplasm can appear, namely an "Arrhenoplasm" or male plasm, and a "Thelyplasm" or female plasm. He maintained further that every metazoön cell (and not merely every reproductive cell) has a sexuality lying somewhere between arrhenoplasm and thelyplasm, but that the actual degree of maleness or femaleness varies in the different groups of cells of which the animal is built up. Moreover, the different parts of the organism were supposed to possess their own sexual determinants, which were believed to be stable from their earliest embryonic foundation. Weininger made no suggestion as to what it is that determines the differentiation of the original protoplasm into arrhenoplasm and thelyplasm, but his idea, though somewhat too morphologically conceived, is useful if only because it emphasises the fact that male and female characters coexist (though they are very unequally represented) in most if not in all diœcious individuals—that is to say, that such individuals are rarely, if ever, wholly male or wholly female. "There may be conceived," he wrote, "for every cell all conditions, from complete masculinity through stages of diminishing masculinity to its complete absence and the consequent presence of uniform femininity."

Weininger drew special attention to the gradations in sexual characters which exist among men and women. There are many men, he remarks, with a poor growth of beard and a weak muscular development, who are otherwise typically males; and so also there are women with ill-developed breasts who in other respects are typical females. There exist all transitional forms from the most masculine male to the most effeminate male, and on the other side, from the sapphist and the virago to the most feminine female; but in man the characters of one sex are always dominant, though the degree of dominance varies through considerable limits. On this view, the phenomena of so-called sexual inversion and homosexuality, which are ordinarily regarded as purely pathological, are in reality psychological manifestations of special characters belonging to the recessive sex.[1]

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[1] Gudger, "The Breeding Habits and the Segmentation of the Egg of the Pipe-Fish, *Siphostoma floridæ*," *Proc. U.S. Nat. Mus.*, vol. xxix., 1905.

[2] Julian Huxley, "The Courtship Habits of the Great Crested Grebe," *Proc. Zool. Soc.*, 1914. Huxley discusses the significance of the process, of which he gives a detailed account. References are given to papers by Selous (*Zoologist*, 1901-02), also describing reversed pairing in the grebe and other birds.

[3] Weininger, *Sex and Character*, English Translation, London, 1906.

Such cases as those cited above have led Castle, Heape, and others to conclude that all animals and plants are potentially hermaphrodite, inasmuch as they contain the characters of both sexes, although ordinarily the characters of one sex only are developed, while those of the other are either latent or imperfectly developed.

Castle has cited cases from among plants in which the characters of one sex can be induced to appear by the artificial destruction of those of the other. Examples of the same kind of phenomenon are supplied by certain animals. Thus Potts[2] has shown that in the male Hermit Crab ova make their appearance in the testes, and the secondary sexual characters become modified in the direction of the female as a consequence of the animal being affected by the parasite *Peltogaster*. Similar changes occur in a number of other animals belonging to widely different groups, but they are especially common in the Crustacea. Geoffrey Smith, who has paid considerable attention to this subject,[3] explained the phenomenon by assuming that the males, in order to cope with the drain on the system caused by the parasites, have to increase their vegetative activity, and that they do this by suppressing their male organisations and calling into play the female ones, which they possess in a latent condition.

In a later paper on the sex-metabolism of *Inachus*, Smith suggested that in the male affected by *Sacculina* the assumption of female characters is due to the formation of a yolk-forming substance (or female generative substance) similar to that normally elaborated in the ovaries, and that this so alters the general nutritive conditions in the direction of the female sex that eventually ova are formed in the gonad. On this view the yolk substance is produced in response to a stimulus set up by the parasite.

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[1] For further information see Krafft-Ebing, *Psychopathia Sexualis*, Stuttgart, 1882; Havelock Ellis, *Studies in the Psychology of Sex: Sexual Inversion*, Philadelphia, 1901; Forel, *The Sexual Question*, English Translation, London, 1908; and Bloch, *The Sexual Life of our Time*, English Translation, London, 1908. For a discussion on the distinctions between men and women, see Manouvrier, "Conclusions générales sur l'Anthropologie des Sexes et Applications sociales," *Rev. de l'École d'Anthropologie de Paris*, 1909; Havelock Ellis, *Man and Woman*, 5th Edition, London, 1914, and Bucura, *Geschlechtsunterschiede beim Menschen, eine Klinisch-physiologische Studie*, Wien, 1913.

[2] Potts, "The Modification of the Sexual Characters of the Hermit Crab, etc.," *Quar. Jour. Micr. Science*, vol. l., 1906. (See p. 326, Chapter IX.)

[3] Smith (G.), "Sex in the Crustacea, etc.," *British Association Report*, Leicester Meeting, 1907; "Studies in the Experimental Analysis of Sex," *Quar. Jour. Micr. Science*, vols. liv. and lv., 1910.

Braem[1] has described an experiment in which he divided into two parts a mature female of *Ophryotrocha puerilis*. After some weeks the head portion regenerated and produced spermatozoa, but the ova almost disappeared. There was no sign of hermaphroditism at the outset, and Braem regards the case as one of change of sex resulting from the altered conditions.

Orton[2] states that in the mollusc *Crepidula fornicata* the males under certain conditions may change into females, thus showing that they have the potentialities of both sexes. The life history of this mollusc has been further investigated by Gould,[3] who shows that the free swimming young, after settling upon older individuals, pass through a series of sexual changes. First they pass through a neutral phase, next they develop into males; then they change into hermaphrodites, and lastly become females. In *Crepidula plana* the individuals only become males if attached at or near a larger individual; otherwise they become females without any transition from the neutral condition.

The marine annelid *Bonellia* displays similar phenomena. The larvæ, after being free swimming, become attached to the sea bottom and develop through a neutral phase into females, or else they establish themselves upon the proboscis of a mature female and become males. Baltzer,[4] by releasing such larvæ before their sex had become completely established and forcing them to lead an independent life, was able to produce grades of intersexual individuals, in which the degrees of maleness or femaleness depended upon the duration of time on which they had been attached before being released.

Potts[5] has adduced evidence that in certain hermaphrodite Nematodes, in Rhabdocœl Turbellarians and in *Rhizocephala* the monœcious condition has arisen through the spermatozoa developing in the ovaries in gradually increasing numbers in successive generations.

Champy[6] has described some interesting experiments on newts,

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[1] Braem, "Ueber die Aenderung des Geschlechts durch äussere Beeinflussung, etc.," *Anat. Anz.*, vol. xxxiii., 1908.

[2] Orton, "On the Occurrence of Protandric Hermaphroditism in the Mollusc *Crepidula fornicata*," *Proc. Roy. Soc.*, B., vol. lxxxi., 1909.

[3] Gould, "Studies on Sex in the Hermaphrodite Mollusc *Crepidula plana*," *Jour. of Exp. Zool.*, I., II., and III., vol. xxiii., 1917, and vol. xxix., 1919.

[4] Baltzer, "Die Bestimmung des Geschlechts nebst einez Analyse des Geschlechtsdimorphismus bei Bonellia," *Mith. Zool. Stat. Neapol.*, vol. xxii., 1914.

[5] Potts, "Notes on the Free-living Nematodes," I., *Quar. Jour. Micr. Science*, vol. lv., 1910.

[6] Champy, "Changement experimentelle du Sexe chez le *Triton alpestris*," *C. R. de l'Acad. Sci.*, vol. clxxii., (9th May) 1921. (See also footnote, p. 700.)

(*Triton alpestris*). He found that if the males were starved severely at a time when spermatogenesis should be active, the development of the secondary sexual characters was arrested, the animals remaining more or less "neuter," as in winter. In the following spring the testes were seen to be replaced by bands of fatty tissue, and the secondary characters did not appear. Two such males which were abundantly fed in the next winter partially assumed the coloration of the female. One was dissected on 11th January, and contained only the fatty bodies which had replaced the testes. Another was kept until 8th April, by which time it had become entirely female in appearance. Each fatty body now contained an ovary with oöcytes, and there was also an oviduct on either side. Moreover, it fostered the fertile eggs of a female with which it had paired some time before.

Crew[1] has described a number of frogs with abnormal reproductive systems, and adduced evidence that these, or some of these, were chromosomally females (XX in composition) which, instead of developing into normal females, became transformed into "somatic" males by the action of some factor or combination of factors which had overridden the chromosome constitution. He points out that the mating of such individuals, functioning as males, must disturb the sex-ratio of the next generation, and that such an interpretation may explain the unusual sex-ratios recorded by various observers.

Julian Huxley[2] had already suggested such a possibility, and applied it statistically to the case of the "millions fish" (*Girardinus pœciloides*) for which the sex-ratio had been found to be abnormal, those bred in the Zoological Gardens, as recorded by Boulenger, being produced in the ratio 3 ♀ : 1 ♂, but subsequently changing to 2 ♀ : 3 ♂, and then later to 1 ♀ : ♂, which last ratio continued for some years and as long as the fish were bred at the Gardens. Huxley has shown that these abnormal ratios can be explained on the assumption of an overriding of the chromosome constitution by means of external influences, the theory as applied to this special case being worked out in some detail.

Boring and Pearl[3] have described hermaphrodite fowls with gonads and external characters as well as sex behaviour in process of changing from a female to a male condition. The ovaries failed to reach complete development, but discharged follicles and luteal cells as well as fully formed spermatozoa are described.

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[1] Crew, "A Description of Certain Abnormalities of the Reproductive Organs found in Frogs, etc.," *Proc. Roy. Physiol. Soc. Edin.*, vol. xx., 1921. See above, p. 663, where the work of Witschi, etc., is referred to; also footnote, p. 700.

[2] Huxley, "Note on Alternating Preponderance of Males and Females in Fish and its Possible Significance," *Jour. of Genetics*, vol. x., 1920. See also "Recent Advances in the Biological Theory of Sex," *Jour. Roy. Soc. of Arts*, vol. lxx., (January and February) 1922.

[3] Boring and Pearl, "Sex Studies," XI., *Jour. of Exp. Zool.*, vol. xxv., 1918. The authors say that the amount of luteal tissue in the ovary is precisely correlated with the degree of external somatic femaleness. Elsewhere they record luteal cells in the testes of hen-feathered males. See also Crew, *Vet. Jour.*, vol. lxxix., 1922.

Bond[1] has given an account of a Formosan pheasant with unilateral development of the secondary male characters and an ovo-testis on the left side, and this bird he is disposed to interpret as having developed from a female zygote in which the sex-factor divided unevenly.

Riddle's experiments on sex-reversal in pigeons and doves have already been referred to, and it was recorded that this investigator obtained various grades of sexual individuals ranging from complete males to complete females, in some of which the sex characteristics might be over-emphasised as by the development of a right oviduct.

Intersexual forms have been described in various insects and notably by Goldschmidt[2] for the gypsy moth *Lymantria*. He crossed two species of this moth, *L. dispar* and *L. japonica*, both of which are strongly sexually dimorphic, and showed that with suitable combinations of different races of these species "intersexes" forming a continuous series passing from complete maleness to complete femaleness could be produced. The results are ascribed to different degrees of potency in the sex-factors, and thus a strictly genetic interpretation was arrived at, but Goldschmidt's latest results with sex-ratios, as Huxley remarks, indicate the probability of moths with the chromosome constitution of one sex having been changed into functional individuals of the other sex.

Huxley refers also to Harrison's[3] results with another species of moth, and to Keilin and Nuttall's[4] account of a graded series of intersexual lice, as well as to the experiments of Hertwig and others, and the records of Pearl and Parshley above mentioned, all of which point in the same direction.[5]

It has already been mentioned that the Free-Martin has been regarded as a partial hermaphrodite. Lillie[6] has shown that during development the vessels of the chorion of the sterile twin anastomose with those of its fellow, which becomes a fertile bull, and that sexual differentiation in the male precedes that of the female. Consequently the male twin exerts an influence over the reproductive system of its fellow at an early stage when the female organs are still undeveloped, and it does this through an internal secretion which is present in the common circulating medium. The growth of the generative organs is thereby partly inhibited in the female twin, while the vestigial male structures are stimulated so as to undergo some development. The Free-Martin, therefore, is an intersexual individual whose development is due to the influence of a hormone elaborated in the male twin, and carried thence to its fellow through a common circulatory system.

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[1] Bond, "On a Case of Unilateral Development of Secondary Male Characters in a Pheasant, etc.," *Jour. of Genetics*, vol. iv., 1914.

[2] Goldschmidt, "Experimental Intersexuality and the Sex Problem," *Amer. Nat.*, vol. l., 1916. For a full account with references to many papers, see Goldschmidt's book referred to above, p. 661.

[3] Harrison, "Genetical Studies in the Moths of the Geometrid Genus *Oporabia*, etc.," *Jour. of Genetics*, vol. ix., 1919.

[4] Keilin and Nuttall, "Hermaphroditism and other Abnormalities in *Pediculus humanus*," *Parasitology*, vol. xi., 1919.

[5] See also Banta, "Sex Intergrades in a Species of Crustacea (*Simocephalus*)," *Proc. Nat. Acad. Sci.*, vol. ii., 1916. Sturtevant, "Intersexes in Drosophila," *Science*, vol. li., 1920. Sexton and Huxley, "Intersexes in Gammarus, etc.," *Jour. of Marine Biol. Assoc.*, vol. xii., 1921; and Bridges, *loc. cit.* (see p. 674).

[6] Lillie (F.), "The Theory of the Free-Martin," *Science*, vol. xliii., 1916; "Sex-Determination and Sex-Differentiation in Mammals," *Proc. Nat. Med. Sci.*, vol. iii., 1917; "The Free-Martin: A Study of the Action of Sex-Hormones," *Jour. Exp. Zool.*, vol. xxiii., 1917.

The fact that the embryos arise from different eggs and not from one, as had been previously suggested, is shown by the presence of two corpora lutea in the ovaries. Assuming Lillie's theory to be correct there is no apparent reason, as Huxley has pointed out, why the ovarian internal secretion of the mother should not penetrate to the fœtuses in any mammal and so produce intersexual individuals, and one can only suppose that there is some special protective mechanism to prevent this from occurring.[1]

Minoura,[2] by removing a portion of the shell from the eggs of fowls during the second week of incubation and transplanting on to the chorio-allantoic membrane a piece of gonad from another individual, has succeeded in producing artificial "Free-Martins" showing varying grades of intersexuality. The grafts were obtained from both other chicks and older birds but the effects were similar. Minoura found that in female-type embryos the right gonad, which normally atrophies, might be got to persist as a result of an ovarian graft.

Hammond,[3] after describing a partially hermaphrodite pig, expresses the view that the development of the accessory genital organs in such cases is under the control of the gonad, which was for the time being better developed or more potent. A similar explanation has been suggested by Stone[4] to account for a comparable condition in a goat.

The experiments on sex-reversal by Steinach, Lipschütz, Pézard, and Sand have been described in an earlier chapter. Sand[1] has recently demonstrated the effects of simultaneous transplantation of a testis and an ovary in an infantile castrated guinea-pig and the grafting of ovaries into the testes of rats or guinea-pigs, and has shown that hermaphrodites with a decided bisexualism of the

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[1] For an account of the "Structures and Homologies of the Free-Martin Gonads," see Willier, *Jour. of Exp. Zool.*, vol. xxxiii., 1921.

[2] Minoura, "A Study of Testis and Ovary Grafts on the Hen's Egg, etc.," *Jour. of Exp. Zool.*, vol. xxxiii., 1921.

[3] Hammond, "A Case of Hermaphroditism in the Pig," *Jour. of Anat. and Physiol.*, vol. xlvi., 1912. *Cf.* Crew, *Vet. Jour.*, vol. lxxviii., 1921.

[4] Stone, "A Typical Male Sex-ensemble in the Domestic Goat," *China Med. Jour.*, (November) 1920. Many other such cases are known.

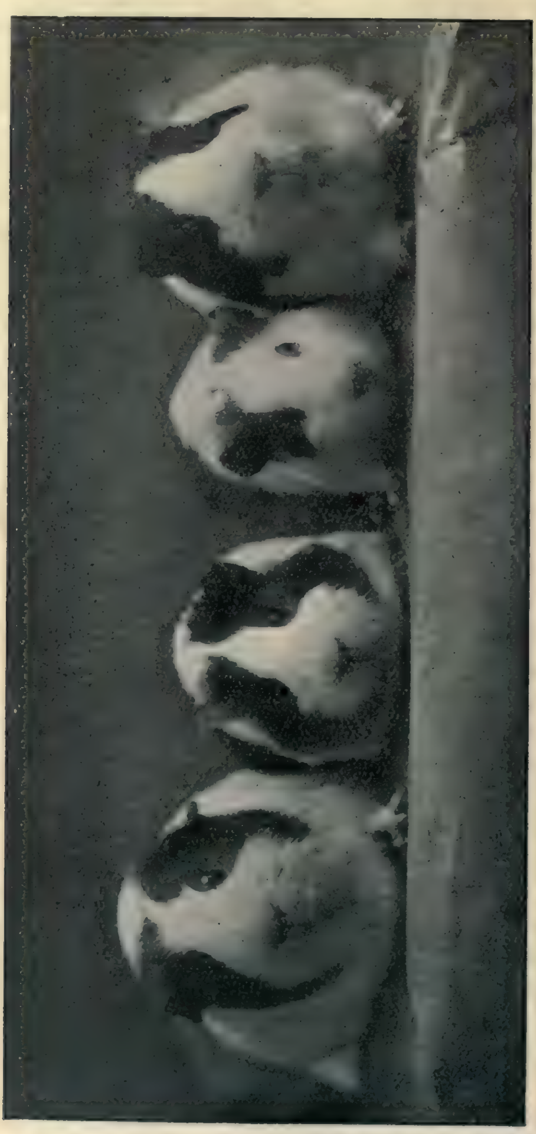

FIG. 170.—Masculinisation of guinea-pig. (From Steinach.) Reading from left to right, the animals are arranged in the following order:—Masculinised female, an ovariotomised sister, a normal sister, a normal brother.

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[1] Sand, "Experiments on the Internal Secretion of the Sexual Glands, especially on Experimental Hermaphroditism," *Jour. of Physiol.*, vol. liii., 1919.

psycho-sexual character could be produced, associated with growth of the mammæ on the one hand and some development of the male organs on the other.

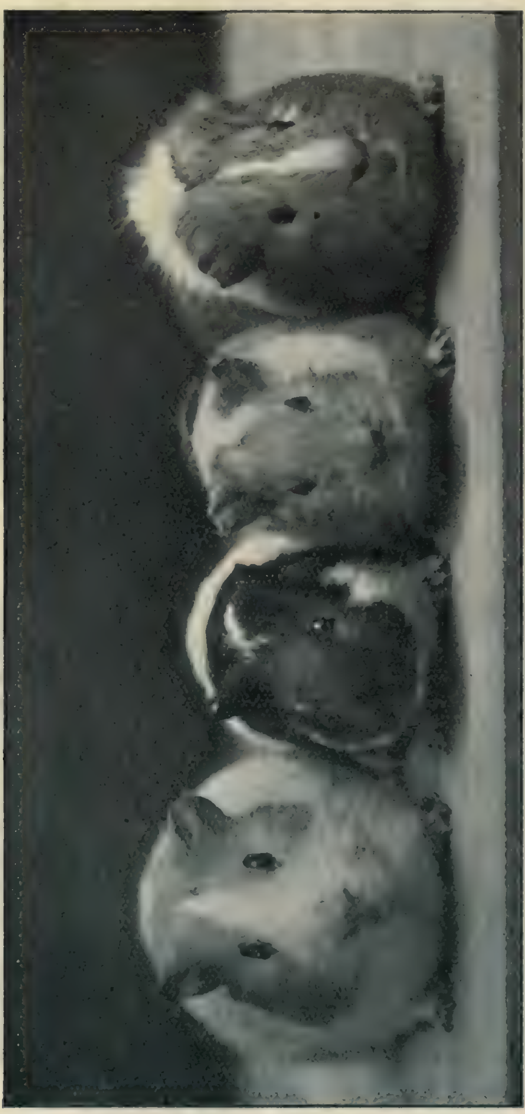

FIG. 171.—Feminisation of guinea-pig. (From Steinach.) Reading from left to right, the animals are arranged in the following order:—Normal male, two feminised brothers, castrated brother.

Moore,[1] working upon rats and guinea-pigs, has obtained results in a general way similar. Like Sand, he has produced artificial hermaphrodites, and thus shown that, contrary to Steinach's conclusions, the gonads do not necessarily act antagonistically. The individuals with the grafts, however, possessed the psychical characteristics of the determined or original sex; thus, while males with ovarian grafts showed great development of the mammæ, the psychical characters were male. With individuals previously castrated the grafts produced a reversal of psychical characters.

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[1] Moore (A.), "On the Physiological Properties of the Gonads as Controllers of Somatic and Psychical Characteristics," I., II., III., and IV., *Jour. of Exp. Zool.*, vol. xxviii., 1919, and vol. xxxiii., 1921.

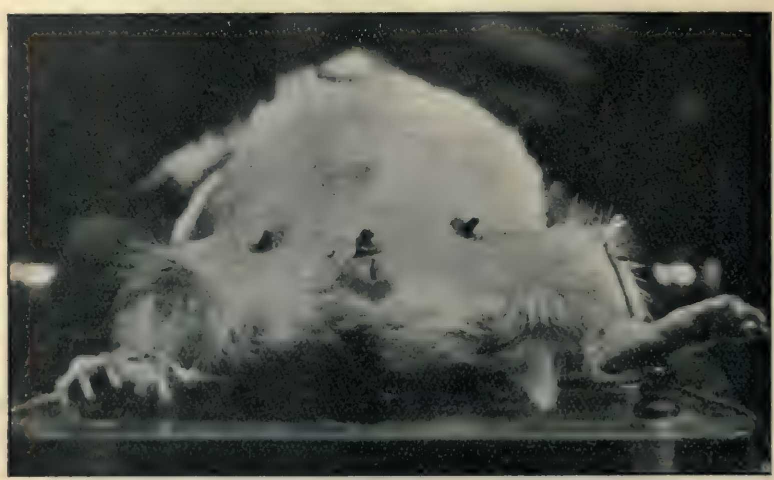

Fig. 172.—Feminised (originally male) guinea-pig with large protruding teats and small penis. (From Steinach.)

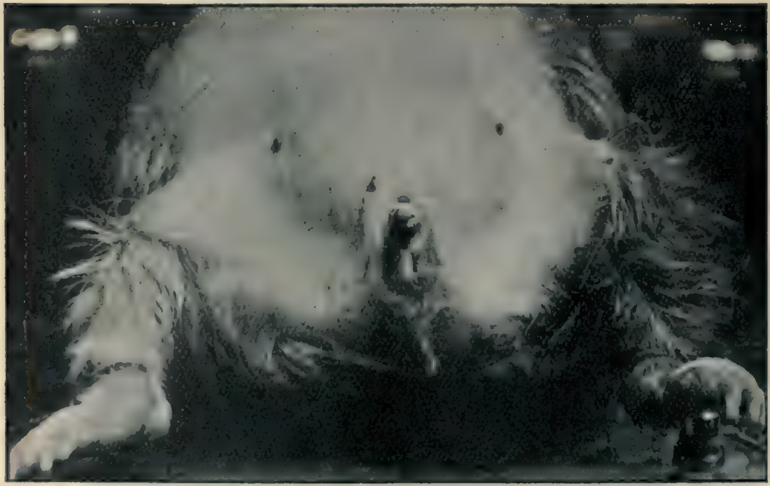

Fig. 173.—Normal male guinea-pig with rudimentary teats and large penis. (From Steinach.)

The effects on growth are noteworthy. After early removal of the gonad the growth curve of the determined male was always higher than that of the determined female. But the difference was accentuated by the presence of an ovary, which thus inhibited the growth.[1]

Pézard's[2] experiments with fowls show that castration and ovariotomy lead to the development of a neutral type. The removal of the testis inhibits the growth of the comb and other erectile structures (wattles and auricular appendages), the capacity to crow and the combative instincts, but it does not affect the spurs on the characteristically male plumage. The latter are inhibited in the hen by the ovarian influence, and as Goodale also has shown, if the ovaries be removed the spurs grow and a brilliantly developed type of plumage is produced, such as one ordinarily associates with the male, but is in reality of a neutral type.

In view of these and other experiments (such as those of Tandler and Keller on oxen, in which the shape of the head is said to be similar in male and female "castrates"), Lipschütz[3] has elaborated the idea of an indifferent or asexual embryonic form which becomes male or female according to whether it is acted on by male or female internal secretions. It will have been seen that whereas in Mammals the fully developed neutral or indifferent type is in its somatic characters much nearer to the female, in birds it is closer to the male. Whether or not this is correlated with the apparent fact that in Mammals the male is heterozygous as regards sex, while in birds the female is heterozygous, is an open question.

General Conclusions

If it be true that all individuals are potentially bisexual (one of the two sexes being recessive or latent excepting in hermaphrodites), and that changed circumstances, leading to a changed metabolism, may, in exceptional cases, even in adult life, cause the development of the recessive characteristics (as in the case of the Crustaceans mentioned above), it would seem extremely probable that the dominance of one set of sexual characters over the other may be determined in some cases at an early stage of development in response to a stimulus which may be either internal or external. The observations which Riddle, Steinach, and others have made upon animals of many different kinds point even to the possibility that sex may be reversed after it has once been established.

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[1] *Cf.* Stotsenburg who found with rats that the testis had no effect on the growth, but that ovariotomy caused an increase of growth by 17-33 per cent. (*Anat. Rec.*, vol. iii., 1909, vol. vii., 1913, and vol. xii., 1917).

[2] Pézard, "Secondary Sexual Characters and Endocrinology," *Endocrinology*, vol. iv., 1920. "Modifications Périodiques ou Définitives des Caractères Sexuels Secondaires et du Comportment chez les Gallinacées," *Annales des Sci. Nat.* (*Secs. Bot. et Zool.*), Paris, 1922.

[3] Lipschütz, "L'Action spécifique de la Secretion interne des Glandes Sexuelles, etc.," *La Revue Scientifique*, Paris, 1921.

It seems certain that sex is not determined by the same factors in all cases, neither is it determined at the same period of development. It may well be that some gametes have an initial tendency to give rise to males and others to give rise to females, and to this extent it is probably legitimate to speak of male and female ova or male and female spermatozoa. Moreover, the conclusion is probably correct that these are developed (at least generally) in simple Mendelian ratios. But it is also probable that no gamete is either purely male or purely female, and it is possible that in some the two kinds of sexual determinants or tendencies are about equally represented.

When once we admit the existence of latent (*i.e.* recessive) sexual characters in individuals in which the characters of one sex are dominant, and that under certain circumstances those of the latent sex can develop at the expense of the dominant ones, in response to appropriate physiological stimuli, we are compelled to acknowledge also that the sex of the future individual is not always predetermined in the gametes or even in the fertilised ovum, but may be called into being at a later stage of life.

Such an admission is of course opposed to some extent to the modern tendency to believe that sex is fixed irrevocably in the fertilised ovum or in the gametes before fertilisation. But while there is evidence amounting to proof that this is the case in some forms of life, it does not necessarily follow that it is true of all Metazoön animals, or even that it is uniformly so of the particular species which have been investigated. On the other hand, many of the facts enumerated above point to the conclusion that the sex of the future organism is determined in different cases by different factors and at different stages of development—either in the unfertilised gamete, or at the moment of fertilisation, or in the early embryo.

Finally, there is evidence that a change in the metabolism, even in comparatively late life, whether induced by castration or the introduction of another gonad or arising primarily from a different cause, may initiate changes in the direction of the opposite sex, or even bring about a complete sex-reversal.[1]

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[1] For a complete review of Champy's work on *Triton*, see Champy, "Étude expérimentale sur les Différences sexuelles chez les Tritons," *Arch. d. Morph. Expér.* (Fasc vii.), 1922. See also Swingle, "Is there Transformation of Sex in Frogs?" *Amer. Nat.*, vol. lvi., 1922. The latter author throws doubt on Witschi's conclusions.

CHAPTER XVI

PHASES IN THE LIFE OF THE INDIVIDUAL—THE DURATION OF LIFE AND THE CAUSE OF DEATH.

"Ταὐτὸν γὰρ ἡβῶντ' ἄνδρα καὶ πρέσβυν θανεῖν ;"—EURIPIDES, *Alcestis.*

THE physiological life of the metazoön individual begins with the union of sperm and ovum, and the organism thus formed thenceforth proceeds to grow. As has been said by Verworn,[1] there is an essential similarity between reproduction and growth, both processes consisting of an increase of living substance. "The difference between that which is usually termed growth in the narrow sense and the phenomenon of reproduction consists only in the fact that in the former case the newly-formed living substance remains in constant connection with the original organism and helps to increase its volume; while in the latter case a part of the substance separates itself from the original organism, either, as in most cases, being set entirely free, or, as in the increase of tissue-cells, being separated merely by a partition wall and remaining in place." Among the more highly organised Protozoa there are various transitional stages between these two conditions.

Growth, like reproduction, involves cell division. As the mass of living substance increases, the cells must multiply, for every cell has assigned to it a limit in size beyond which it cannot pass. Cell division goes on, though with gradually decreasing frequency, throughout practically the whole of life; tissue formation continues, but from an early period of development onwards there is a progressive diminution in the power of growth. Increase in the number of cells is, however, specially characteristic of the embryonic period. In the later stages of development growth occurs in great measure through cell enlargement and the deposition of intercellular substance.

Minot has compared the growth of the body to a man building a wall.[2] "He begins at first with great energy, full of vigour; the wall goes up rapidly; and as the labour continues, fatigue comes into play. Moreover, the wall grows higher, and it takes more effort and time to carry the material up to the top of the wall, and to continue to raise its height, and so, as the wall grows higher and higher, it grows more slowly and ever more slowly, because the obstacles to be overcome have increased with the very height of the wall itself. So it seems with the increase of the organism, and with the increase of our development, the obstacles to our growth increase." According to Minot, the explanation of this phenomenon must be sought in the differentiation of the protoplasm, which goes on growing with an ever-increasing complexity as the cells of the body multiply.

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[1] Verworn, *General Physiology*, Lee's Translation, London, 1899.

[2] Minot, "The Problem of Age, Growth, and Death." *Popular Science Monthly*, vol. lxxi., 1907; reprinted London, 1908.

It has just been mentioned that every cell has assigned to it a definite limit in size beyond which it cannot go. Boveri[1] has enunciated the general law that the process of cell division is regulated by the proportion of chromatin material to cytoplasm, and that it comes to a standstill when the ratio of the mass of chromosomes to that of the cells in any given tissue or organ reaches a certain definite point. Furthermore, it is stated that the size of the cells in any given tissue after active cell multiplication has ceased, bears a definite relation to the original mass of chromatin contained in the fertilised egg.[2] Thus it is pointed out that the mesenchyme cells of the embryo developed from the artificially fertilised sea-urchin's egg are only half the size of those of the embryo which has been produced by normal fertilisation, for although the parthenogenetic and normally fertilised eggs are equal in size at the commencement of segmentation, the latter possess initially twice as much nuclear substance as the former.[3]

The fact that cell division ceases when the ratio of the mass of chromosomes in the nuclei of an egg (or of a tissue or organ) to that of the surrounding protoplasm reaches a certain definite limit, is regarded by Loeb[4] as evidence that this ratio is determined by the laws of mass action and chemical equilibrium. He says further that if this conclusion is correct the synthesis of nuclein compounds, from their protoplasmic constituents, must be a reversible process.

The fertilisation of an ovum is immediately succeeded by an enormous synthesis of nuclear material. In the cellular division which follows, each new nucleus is of the same size as the parent

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[1] Boveri, *Zellen-Studien*, Part V., Jena, 1905.

[2] Robertson, "On the Normal Rate of Growth of an Individual and its Biochemical Significance," *Arch. f. Entwick.-Mech.*, vols. xxv. and xxvi., 1908. "Studies in the Growth of Man," *Amer. Jour. of Phys.*, vol. xxxvii., 1913. See also Feldman, *Principles of Ante-Natal and Post-Natal Child Physiology*, London, 1920.

[3] Driesch, "Über das Mesenchym von unharmonisch zusammengesetzten Keimen der Echiniden," *Arch. f. Entwick.-Mech.*, vol. xix., 1905.

[4] Loeb, *The Dynamics of Living Matter*, New York, 1906.

nucleus. From this fact Loeb[1] concludes that the nucleus itself, or one of its constituents, acts as a catalyser in the synthesis of nuclein in the fertilised ovum. Robertson,[2] quoting partly from Loeb, writes as follows: "If the mass of the original fertilisation nucleus be m, the mass of nuclear material increases during the first segmentation period to $2m$, during the next to $4m$, and so on in geometrical progression. The duration of the various periods of segmentation, however, matters very little. Hence in the first unit of time after the beginning of cell division, a mass m of nuclear material is formed, in the second a mass $2m$, in the third a mass $4m$, and so on; thus the velocity of the synthesis *increases* with lapse of time and with the mass of nuclear material already formed. This is a characteristic of that class of reactions known as autocatalytic, in which one of the products of the reaction, or, in this case, one of the constituents of the nucleus, accelerates the reaction. During the process outlined above, an emphatic disproportion between nuclear and protoplasmic material has been established. As the nuclear synthesis becomes slower, however, the disproportion tends to adjust itself until, finally, the growth of the organism consists almost entirely of the growth of protoplasmic material, and in the final re-establishment of the equilibrium between cytoplasm and nuclear material."

Robertson has investigated mathematically the quantitative relations which exist between the amount of growth and the time of growth. He concludes that there are two or more growth cycles representing autocatalytic processes which make up the total growth of an individual. In man there are three maxima of rate of growth, representing three phases or growth cycles. One of these is intra-uterine, but it is probable that this is not quite complete at birth. The second growth cycle seems to attain its maximum annual increment at about the fifth year, since the increment in weight at that age, as deduced from an investigation on growth in English boys, considerably exceeds the annual increments for the years immediately following. A third maximum in yearly increments occurs in males at about the sixteenth year, that is, at about the time of puberty. In the rat, according to Donaldson,[3] there are two intra-uterine growth cycles, while there is only a single well-defined extra-uterine cycle. Robertson suggests that the first growth cycle in Mammals represents the course of the autocatalytic synthesis of the nuclear substance, that the third cycle represents the period during which cytoplasmic material is built up, while the second growth cycle is intermediate, representing a time when both synthetic processes go on contemporaneously.

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[1] Loeb, "Weitere Beobachtungen über den Einfluss der Befruchtung, etc.," *Bio. Chem. Zeitsch.*, vol. ii., 1906. "The Chemical Character of the Process of Fertilisation and its Bearing on the Theory of Life Phenomena," Seventh Internat. Congress, Boston, University of California Publications, vol. iii., 1907.

[2] Robertson, *loc. cit.*

[3] Donaldson, "A Comparison of the White Rat with Man in respect to the Growth of the Entire Body," Boas Anniversary Volume, *Anthropological Papers*, New York, 1906.

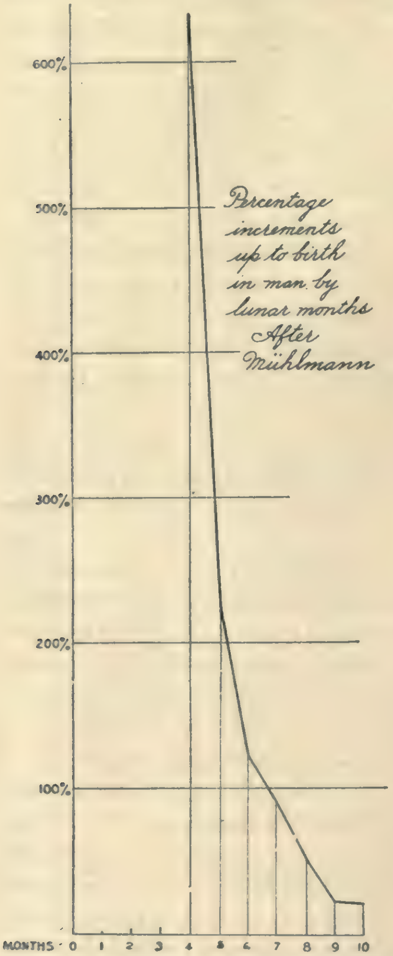

Fig. 174.—(From C. S. Minot's *Problem of Age, Growth, and Death*, G. S. Putnam & Sons, and John Murray.)

Growth of the Body before Birth

Minot[1] has recorded the results of weighing embryo rabbits at different stages of development with a view to determining their rate of growth. The results showed that in the period from the ninth to the fifteenth day the young rabbit adds on an average 704 per cent. to its weight daily, and that in the period from the fifteenth to the twentieth day, the average daily addition is only 212 per cent. It may be assumed, therefore, that in younger embryos (before the ninth day) there is an increase of over a thousand per day. Minot estimates that over ninety-eight per cent. of the original power of growth of the rabbit or the chick has been lost at the time of birth or hatching, and that a similar fact is equally true of man. "We start out at birth certainly with less than two per cent. of the original growth power with which we were endowed. Over ninety-eight per cent. of the loss is accomplished before birth—less than two per cent. after birth." The accompanying diagram represents roughly the rate of growth in man before birth. The time intervals correspond to the ten lunar months of gestation. The rate of increase in the first three months is not indicated, since there are no statistical data on which to found any knowledge, but from the third month onwards there are a few records available. The diagram shows that from the third to the fourth month the increase in growth is 600 per cent., after which it quickly drops until, during the last month of pregnancy, it is barely twenty per cent.

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[1] Minot, *loc. cit.*

Growth of the Body after Birth

The rate of growth from birth to maturity has been investigated most fully by Minot[1] in the case of the guinea-pig. When this animal is born it is far advanced in development, the period of gestation being unusually long. Immediately after birth there is a lessening in the power of growth, a fact which Minot ascribes to the physiological shock from which the organism suffers as a consequence of being born. After two or three days, however, the young are fully recovered, and are capable of adding over five per cent. to their weight in a single day. By the time they are seventeen days old they are only able to add four per cent. to their weight, and by the time they are twenty-four days old, less than three per cent. When they have been born forty-five days, they can add only a little over one per cent. to their weight; when ninety days old, less than one per cent., and still less as they grow older, until when about a year old they attain their full size. The curves in the accompanying diagrams show the daily percentage increments in weight in male and female guinea-pigs respectively, as ascertained by Minot. It is seen that the curve for the females is very similar to that for the

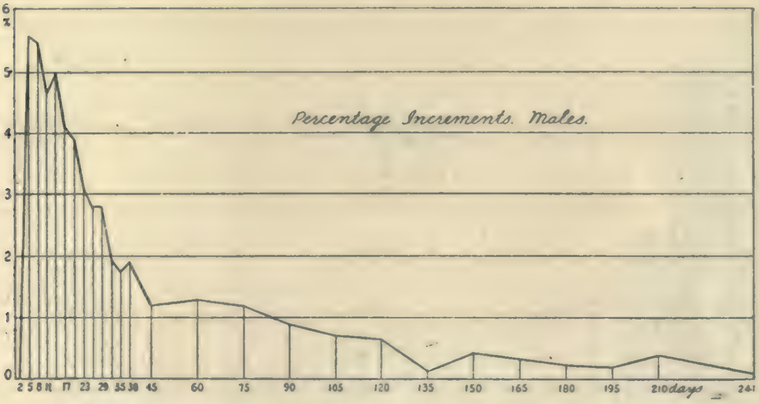

FIG. 175.—(From Minot's *Problem of Age, Growth, and Death*, G. S. Putnam & Sons, and John Murray.)

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[1] Minot, "Growth and Senescence," *Jour. of Physiol.*, vol. xii., 1891. "Age, Growth, and Death," *Popular Science Monthly*, vol. lxxi., 1907.

males. Both show an early period of rapid decline in which the rate of growth is quickly diminishing, followed by a period of slight decline in which the curve is still falling, but very much more gradually (Figs. 175 and 176).

Minot has also investigated the rate of growth in the rabbit and in the chicken. The young rabbit, as is well known, is born in a very immature state of development after a relatively short gestation period. Correlated with this fact, it was found that the male rabbit four days after birth is capable of adding over seventeen per cent. to its weight in a single day. From that time the percentage increment drops very rapidly, so that at an age of twenty-three days the rabbit can only add a little over six per cent. After about the fifty-fifth day the decline in the growth rate, which has hitherto been rapid, becomes more gradual. In the case of the chicken, Minot's results were in a general way similar, but the rate of growth on the first day it could be measured was a nine per cent. addition to the weight, while the change from the initial rapid decline to the subsequent slow decline was more gradual than in the other two animals.[1]

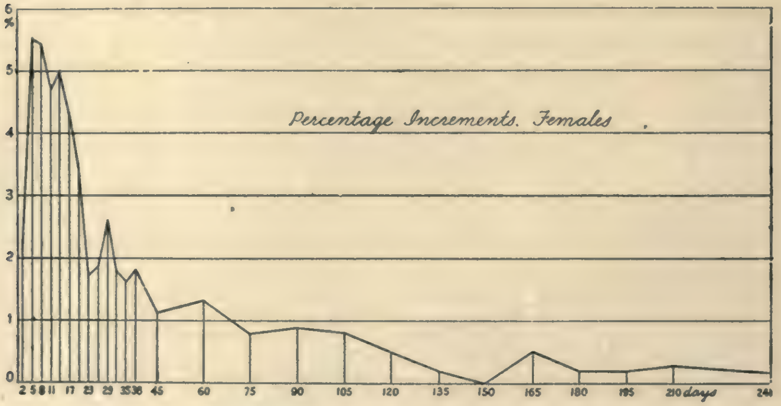

FIG. 176.—(From Minot's *Problem of Age, Growth, and Death*, G. S. Putnam & Sons, and John Murray.)

The mean weight of the foal at birth is said to be 112 lbs. During the first three months the average daily increase is 2·2 lbs.; from three up to six months it is 1·3 lbs.; and from six months up to three years 0·7 lb. It is said that probably many horses continue to grow until they are six years old.[2]

The calf at birth weighs about 77 lbs., and the average daily increase during the first two years is 1·5 lbs. With the sheep the increase is greater, for a young lamb in ten days can add fifty per cent. to its original weight, and can double it at the end of the first month, and treble it at the end of the second. In pigs, however, the increase is even more rapid, for a young pig can add twenty per cent. to its original weight by the end of the first week, and up to the end of the first year can add an average daily increase of 0·44 lb.

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[1] For an exhaustive account of the growth phenomena in the rat, in which the growth curve is in a general way similar to that of the rabbit, see Donaldson, *The Rat* (Wister Institute Memoirs, No. 6), Philadelphia, 1915.

[2] Smith (F.), *Veterinary Physiology*, 3rd Edition, London, 1907.

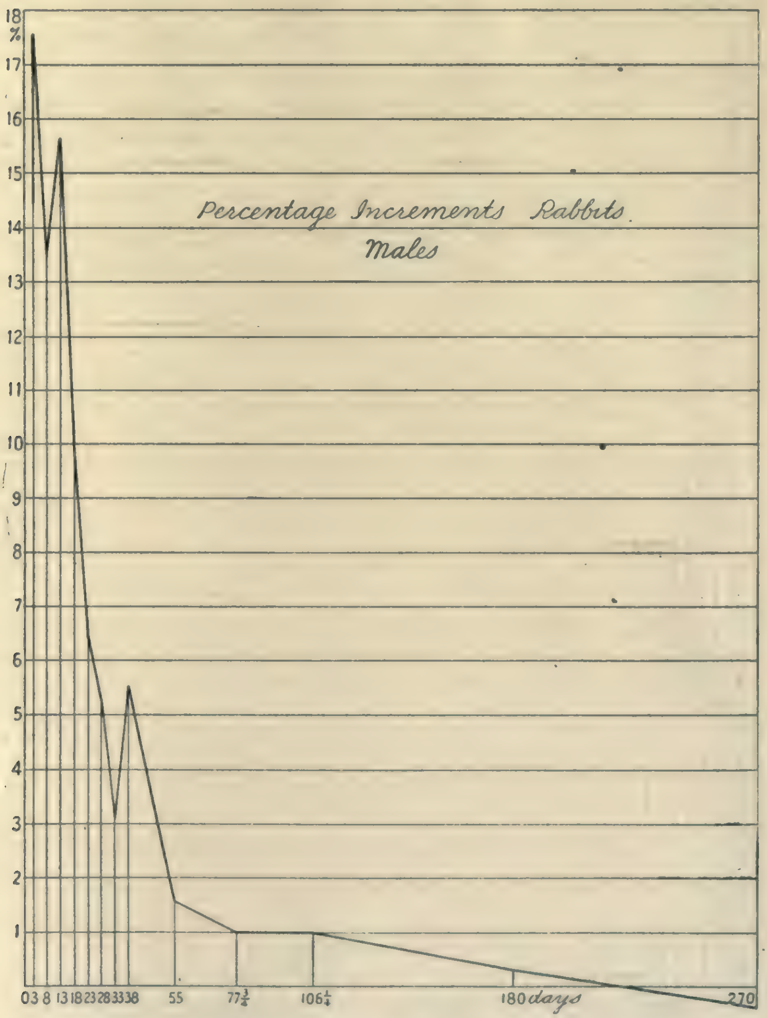

FIG. 177.—(From Minot's *Problem of Age, Growth, and Death*, G. S. Putnam & Sons, and John Murray.)

Murray,[1] who has investigated the laws of growth in various animals, finds that whereas the growth of sheep, rabbits, and chickens appears to conform to a general principle which may be expressed as a simple formula, and represented in a simple curve, with cattle there is evidence of an acceleration in the rate of growth between the first and second year, similar to the prepubertal acceleration in man described below and shown in the diagram (Fig. 182). Murray

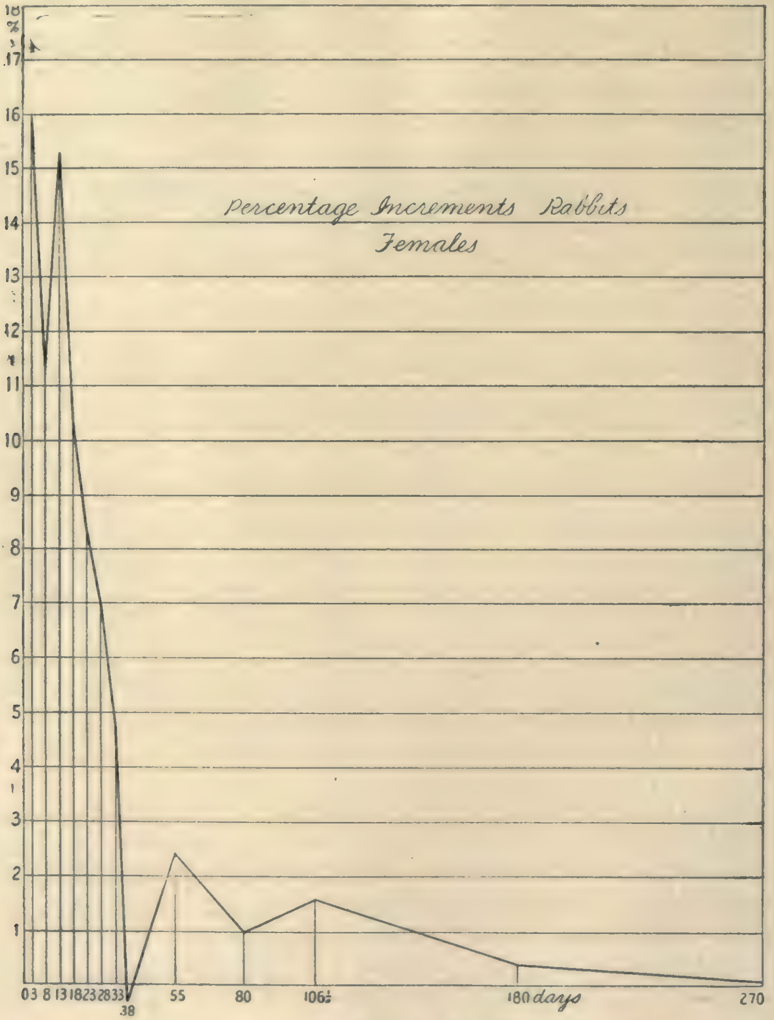

Fig. 178.—(From Minot's *Problem of Age, Growth, and Death*, G. S. Putnam & Sons, and John Murray.)

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[1] Murray, "Normal Growth in Animals," *Jour. of Agric. Science*, vol. xi., 1921.

points out that if there is a second period of acceleration in cattle at about the age of sixteen or seventeen months, of which evidence is adduced, this period would be the most economic one for slaughtering for beef, especially if the animals can be brought to the desired condition of fatness at the same time.

Mackenzie and the present writer[1] have shown that the most economic state of fatness in which to slaughter cattle is that represented by an average carcass-to-liveweight percentage of about fifty-six—and that this condition can be well attained at the age in question. Very fat beasts are produced at a cost of much waste, and owing to the excess of "offal" or internal fat removed with the alimentary canal and other parts, their carcass percentage is apt to be lower than with beasts whose condition is poorer. Hammond,[2] who has made a close study of the biometry of growth in various breeds of domestic animals, makes a similar statement for sheep.

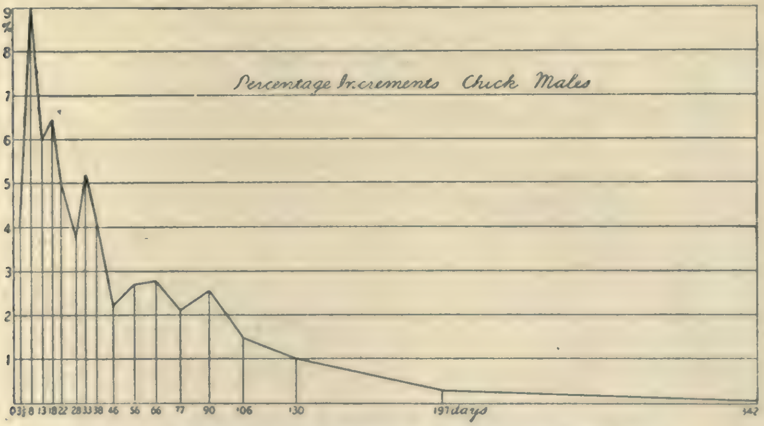

FIG. 179.—(From Minot's *Problem of Age, Growth, and Death*, G. S. Putnam & Sons, and John Murray.)

In man growth is most rapid during the first year of life, when a child is able to increase its weight by 200 per cent. For the second year this percentage drops to twenty, and for subsequent years up to about the age of thirteen, it fluctuates around ten, showing a gradual tendency to decrease (but *cf.* Robertson, quoted on p. 703). After this there is a distinct increase in the percentage increment representing the prepubertal and pubertal growth. Then there is a further decline in the power of growth, which gradually diminishes. The prepubertal growth of girls usually precedes that of boys, so that between the ages of twelve and fifteen girls are often heavier and taller than boys. Boys grow most rapidly at sixteen, girls at thirteen or fourteen. Boys attain their full height at from twenty-three to twenty-five years of age; girls at twenty or twenty-one. In both sexes the weight of the body tends to increase until about the fiftieth year or somewhat later, owing to an accumulation of fat, but there are of course very many exceptions.[1]

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[1] Mackenzie and Marshall, "Beef Production" (Abstract), *Jour. Board of Agric. and Fisheries*, vol. xxv., 1918. See also chapter on Physiology in Mackenzie's *Cattle*, Cambridge, 1919.

[2] Hammond, "On the Relative Growth and Development of Various Breeds and Crosses of Cattle," *Jour. of Agric. Science*, vol. x., 1920; and "On the Relative Growth and Development of Various Breeds and Crosses of Sheep," *Jour. of Agric. Science*, vol. xi., 1921. These papers contain a full account of the literature.

That good nourishment and a healthy environment favour growth is a fact recognised by all. So also systematic exercise has been found to increase both the weight and the height,[2] and it has been shown further that well-developed children are more efficient mentally and take better places at school than ill-developed and badly-nourished ones.[3]

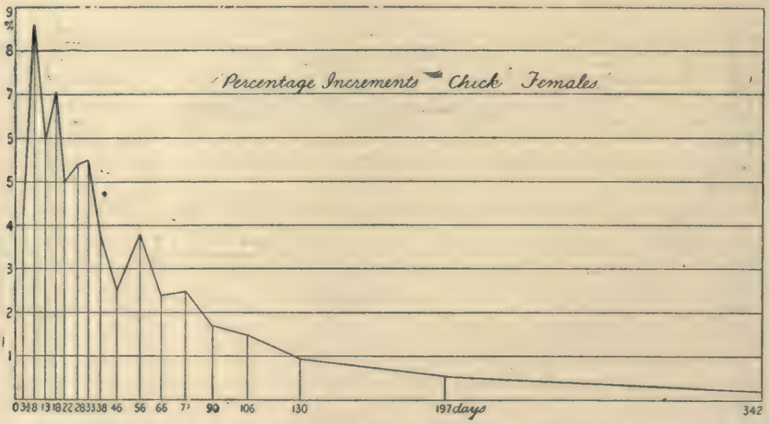

FIG. 180.—(From Minot's *Problem of Age, Growth, and Death*, G. S. Putnam & Sons, and John Murray.)

In horses and other domestic animals the effects of feeding on growth and general development are remarkable. Thus it is said that a highly-fed thoroughbred at two years old is "furnished" and looks as old as an ordinary horse at four years old.[4]

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[1] See Minot, *Popular Science Monthly*, vol. lxxi., 1907. Minot states that his calculations are based on data supplied by Professor Donaldson. See also Lee, Article "Reproduction," in Howell's *American Text-book of Physiology*, 2nd Edition, London, 1900.

[2] Beyer, "The Influence of Exercise upon Growth," *Jour. of Exp. Med.*, vol. i., 1896.

[3] Porter, "The Physical Basis of Precocity and Dulness," *Trans. Acad. of Science*, St. Louis, vol. vi., 1893.

[4] Smith, *loc. cit.* For growth in pigs, see Hammond, *Jour. of Agric. Sci.*, 1922.

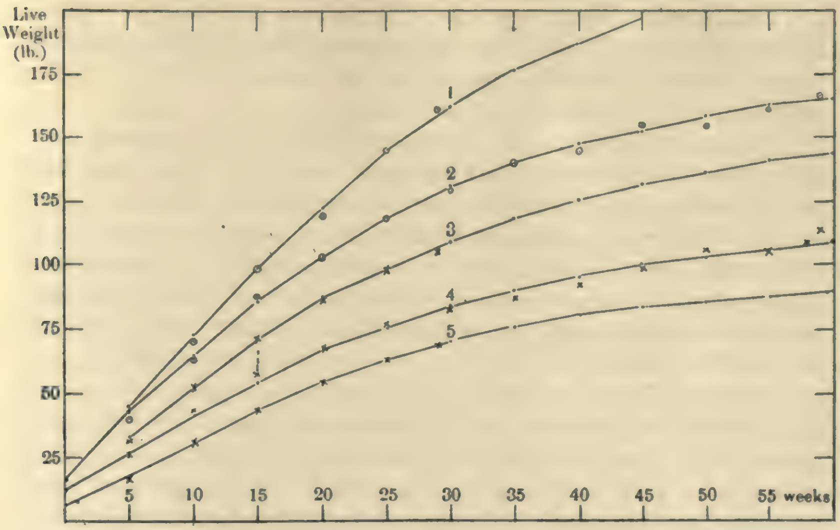

FIG. 181.—Growth of sheep. (From Alan Murray, *Jour. of Agric. Science.*)

Curve 1, Suffolk sheep (males, single).
„ 2, „ „ (females, single).
„ 3, Shropshire + Merino sheep (males, single).
„ 4, „ „ „ (females, single).
„ 5, „ „ „ („ twins).

The weights actually observed are indicated by ⊙ for the Suffolk, and + for the Shrop.-Merino sheep.

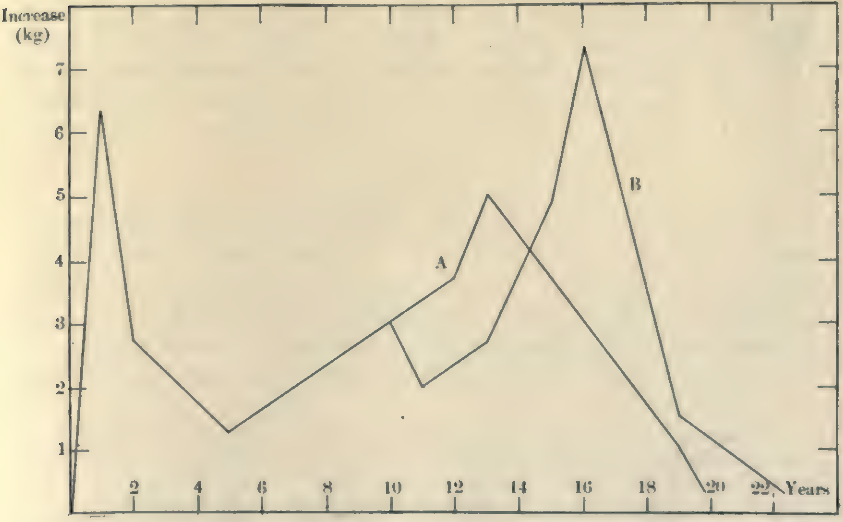

FIG. 182.—Growth of girls (A) and boys (B); increase kg. per annum. Prior to the tenth year the rate of growth of the two sexes is represented by the same line. (From Alan Murray, *Jour. of Agric. Science.*)

The various other external factors that influence growth in animals of different kinds are discussed by Morgan in his work on "Experimental Zoology,"[1] to which the reader is referred for an account of the literature of the subject.

The internal factors or conditions which control growth have been recently investigated by Robertson and Ray,[2] who show that early growth in mice is due to over-increase of the cellular elements or parenchymatous tissue, as distinguished from the sclerous or connective tissues. They state that early overgrowth is correlated with longer life, the individuals displaying it being highly resistant to external disturbing factors and tending towards a relative paucity of tissue accretion late in life. Short-lived individuals, on the contrary, are relatively unstable and sensitive to external influences, and tend to display a relatively deficient early growth but rapid and unstable accretions of connective tissue elements in late life. Such accumulations are notoriously characteristic of old age, and their presence throws a strain on the metabolism of the cellular elements which support these accretions, and consequently tend to shorten life. The administration of tethelin or cholesterol, which was found to prolong life, led to an increased anabolism of the distinctively cellular elements to the disadvantage, in the competition for nutriment, of the connective tissue. If tethelin was given to mice only so long as they were immature, the cessation of this stimulus was followed by a great increase in size. Such increase was due to the growth of the sclerous tissue, and added to the already highly developed cellular tissue (hitherto not noticeable) resulted in gigantic individuals. It was shown also that brain tissue from which the cholesterol had been extracted was without effect upon growth, whereas nervous tissues not so treated stimulated anabolism.

PUBERTY

Puberty, or the period at which the organism becomes sexually mature, is marked by the occurrence of those constitutional changes whereby the two sexes become fully differentiated. It is at this period that the secondary sexual characters first become conspicuous, and the essential organs of reproduction undergo a great increase in size,[3] while in those animals in which during immaturity the testicles remain within the body cavity, it is at puberty that these organs first descend into the scrotal sacs. The puberty acceleration in growth which takes place in man has been already referred to. This change is accompanied, as is well known, by alterations in the general proportions, associated with an increase of strength, a deepening of the voice, and a growth of hair on the face and other parts of the body, processes which are not completed until about the twenty-fifth year.[1] In temperate climates puberty begins in boys at about the fourteenth or fifteenth year; in tropical countries it is usually a few years earlier.[2] It is at this period that ripe spermatozoa first make their appearance in the seminal fluid, which is henceforward secreted in considerable quantity.

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[1] Morgan, *Experimental Zoology*, New York, 1907. See also Robertson and Ray, "Experimental Studies on Growth," *Jour. of Biol. Chem.*, vol. xxiv., vol. xxv., 1916, and vol. xxxvii., 1919.

[2] Robertson and Ray, "Experimental Studies of Growth," XV. and XVI., *Jour. of Biol. Chem.*, vols. xlii. and xliv., 1920. For Child's views on growth, see above, p. 225.

[3] Disselhorst, "Gewichts und Volumszunahme der männlichen Keimdrüsen, etc.," *Anat. Anz.*, vol. xxxii., 1908.

In women puberty occurs at a slightly earlier age than in the male sex. The constitutional changes characterising this period take place more suddenly in the female, the girl almost at once becoming a woman, whereas the boy is several years before he develops into a man, complete maturity not being reached until the twenty-fifth year. Moreover, the onset of puberty in the girl is marked more precisely by the coming of menstruation, which may make its appearance in temperate climates in the thirteenth year. At about the same time the pelvis widens, and the other characteristic anatomical changes take place; the subcutaneous layer of fat, the development of which assists so largely in giving the body its graceful contour, is deposited; while the internal generative organs enlarge and ripe ova are produced by the ovary.[3]

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[1] The breaking of the voice occurs to a certain extent also in girls but less sudden. Appended is Barth's table of the length of the vocal cords at different ages (as quoted from Feldman, *Ante-natal and Post-natal Child Physiology*, London, 1920).

Age in years - - -	0	2	6	10	14	20	30
Males, mm. - - -	6	8	10	13	13	24	30
Females, mm. - -	6	8	10	12	12	16	20

It is thus seen that the lengthening of the cords even in boys is not absolutely sudden but extends over years.

[2] Havelock Ellis, *Man and Woman*, 5th Edition, London, 1914. This book contains a wealth of information concerning growth, etc., and many other matters. Steinach and Kammerer, "Klimak und Mannbarkeit," *Arch. f. Entwick.-Mech.*, vol. xlvii., 1921.

[3] Runge (E.), however ("Beitrag zur Anatomie der Ovarien Neugeborener und Kinder von der Pubertätzeit," *Arch. f. Gynäk.*, vol. lxxx., 1906), states that growing follicles are by no means uncommon in ovaries of young children. In the first year of life he found follicles of considerable size, and in the second year still larger ones, some having a diameter of 135 μ. In the third year degenerate follicles were also found. During this and the following years there was a progressive increase in the size of certain of the follicles until the ovaries became scarcely distinguishable from those of adults excepting for their smaller

In both sexes the purely physical changes of puberty are accompanied by psychical ones which are no less pronounced. Both kinds of change are dependent largely, if not entirely, upon the functional development of the generative glands.[1]

In animals the general nature of the change which sets in at puberty is similar to that occurring in the human species, and the secondary sexual characters often appear for the first time at this phase of life. Excepting in the case of the domestic animals, little is definitely known concerning the respective ages at which the different species become mature. Most fillies come in use within two years, and all by the time they are three. Cows may come on heat when a year old, but it is best to postpone service until three months later. A good deal depends on nutrition, but even starved and backward cows will receive the bull when fifteen months old. Sows will receive the boar when six months old, and sometimes two months earlier. Sheep will breed at the age of six months (that is to say, lambs born in the spring will breed in the following autumn), but the practice is to be deprecated in the interests both of the ewes themselves and of their lambs. Dogs will breed when about ten months old or even earlier (sometimes seven), but the larger kinds do not breed so soon. Cats are similar. Rodents may breed when still younger, but whether they do so or not depends upon the season of the year and other conditions of environment and nutrition. The white mouse is stated to breed when six weeks old,[2] the white rat at about two months,[3] and the domesticated rabbit at about five months.

It should be remembered that in animals as in man complete sexuality is not acquired all at once in either sex. Thus, in actual practice, ram lambs are not allowed to serve more than 20 or 25 ewes in a season, as against 40 or 50 which older rams may serve. Similarly with stallions, a yearling may serve 15 mares in a season, a two-year old 60, while an adult may serve 80 to 120 mares.

THE MENOPAUSE

In the male sex (as already mentioned) there is no definite age at which the reproductive functions cease. In the female, on the

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size. Runge states further that in one instance he found a corpus luteum in an ovary of a recently born child, but this must be regarded as very exceptional. As a result of his observations, Runge concludes that follicular maturation sets in during infancy and not at puberty. Ovaries of human embryos showed growing follicles only in very rare instances.

[1] For further extensive information see Stanley Hall, *Adolescence*, New York, 1904.

[2] Kirkham, "The Life of the White Mouse," *Proc. Soc. Exp. Biol. and Med.*, vol. xvii., 1920.

[3] Donaldson, *loc. cit.* Evans and Bishop state that the first œstrus occurs between the thirty-seventh and fifty-fifth day ("On the Relations between Fertility and Nutrition," *Jour. of Metabolic Research*, vol. i., 1922).

other hand, the close of the reproductive period is far more definite, and it is this change in the human female which constitutes the menopause or climacteric. The essential phenomenon of the menopause, therefore, is the permanent arrest of all the functions connected with reproduction.[1] It is the inversion of the developmental process of puberty, and marks the termination of active sexual life. In temperate climates it almost always takes place between the ages of forty and fifty, and most usually at about the age of forty-five.[2] In warm countries it has a tendency to be earlier, and in colder ones later. It is usually earlier among the labouring classes, and also in women in whom puberty was early. The actual duration of the period when menopause symptoms occur varies from about three to five years.

The symptoms of the menopause may be referred to two stages—(1) a stage of menstrual irregularity, and (2) a post-cessation stage, during which various systemic disturbances are wont to occur. During the latter period especially the organic functions are irregular. Palpitation, dyspepsia, sweating, and vasomotor changes are not infrequent, and neurasthenic phenomena, hysteria, and other psychic disturbances sometimes occur, accompanied by neuralgia, rheumatism, and various disorders. Mental instability at the "change of life" is not uncommon. It is well known that the menopause is followed by profound psychological changes which vary in different individuals. The changes which take place in the lower Mammals have not been studied, but they can hardly be so great as those which occur in women.

The anatomical and physiological basis of the menopause is, as already indicated, the atrophy of the reproductive organs. The following are the changes which take place in women:—

(1) Senile changes in the ovary: (*a*) Atrophy, induration, and shrinkage to the size of the rudimentary ovary; (*b*) disappearance of Graafian follicles and cessation of ovarian functions.

(2) Senile changes in the Fallopian tubes: (*a*) Shortening and narrowing, often accompanied by obliteration of the lumen; (*b*) destruction of the epithelial cells.

(3) Senile changes in the uterus: (*a*) Atrophy of the entire organ, which may be reduced to a hard, wedge-shaped body, one-quarter the size of the functional organ; (*b*) in many cases closure of the internal os, or of the external os, or complete obliteration of the canal; (*c*) consequent secretions producing pyometra or hydrometra,

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[1] Cases are on record, however, of women conceiving some years after the apparent menopause.

[2] For further details see Kelly, *Medical Gynecology*, London, 1908; and Luciani, *Human Physiology*, English Edition, vol. v., London, 1921.

due to the locking up of the secretions; (*d*) in some cases the disappearance of the vaginal portion, making the upper part of the vagina continuous with the uterine canal; (*e*) degeneration of the muscular and glandular elements; and (*f*) cessation of menstruation.

(4) Senile changes in the vagina: (*a*) Shortening, narrowing, and loss of elasticity; (*b*) loss of pavement epithelium, and substitution of a hard surface containing cicatricial tissue; and (*c*) contraction of the entrance to the vagina.

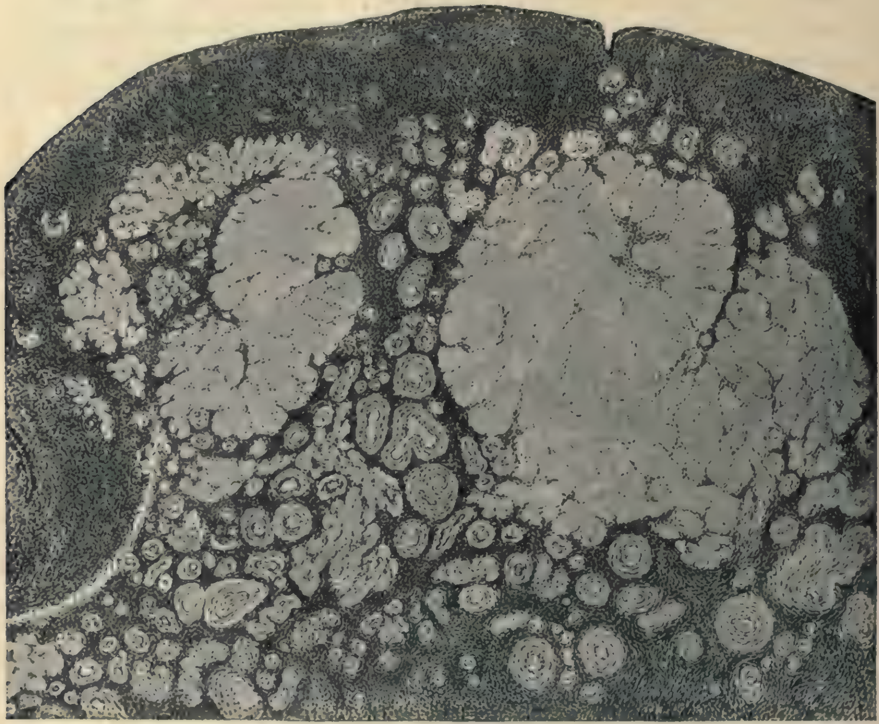

Fig. 183.—Section through ovary of woman of fifty-six, showing degeneration of follicles and sclerosis of connective tissues. (From Sellheim.)

(5) Senile changes in the vulva: (*a*) Great contraction and loss of elasticity; (*b*) destruction of glands and follicles; and (*c*) cutaneous surface becoming dry and scaly.

(6) Senile changes in the mammary glands: (*a*) Loss of glandular elements and cessation of function; and (*b*) shrinkage due to atrophic loss, which, however, is sometimes compensated for by a deposition of fat.[1]

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[1] Dudley, *The Principles and Practice of Gynæcology*, 4th Edition, London, 1905. For a further account of the atrophic changes in the uterus and other generative organs, see Sellheim.

Other changes, depending probably on the degeneration of the ovaries, are the assumption of certain of the secondary male characters. These are apparently more marked in some animals than they are in the human species, and have already been mentioned in dealing with the internal ovarian secretions (p. 340).

The ages at which domestic animals cease to breed have been only imperfectly determined since they generally die before reaching their climacteric. Mares have been known to produce young beyond thirty years,[1] sheep up to twenty, and cats to fourteen, but they may cease somewhat earlier and yet maintain a healthy existence for a few years.[2] Kirkham[3] says the white mouse stops reproducing at eighteen to twenty-two months after having twelve to sixteen litters. The menopause in the white rat occurs at the age of fifteen to eighteen months.[4]

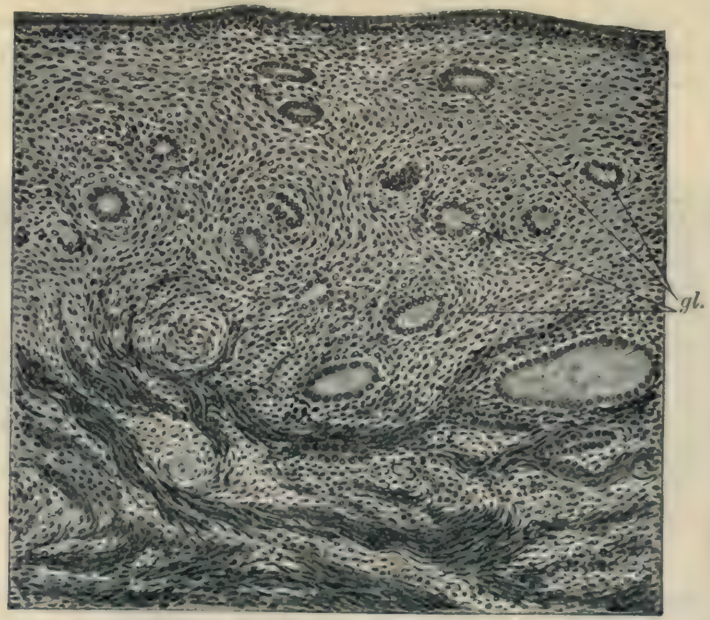

FIG. 184.—Section through uterine mucous membrane of woman of sixty. (From Sellheim.) *gl*, Glands.

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[1] Wood (W. A.) found that out of 1216 thoroughbred mares recorded in the earlier volumes of the *General Stud-book*, one bred at 33, two at 30, four at 29, seven at 28, and seventeen at 27. He draws the conclusion that in actual practice the mare generally continues to breed as long as she lives ("Note on the Breeding Age of Thoroughbred Mares," *Vet. Jour.*, December 1921).

[2] Fleming, *Veterinary Obstetrics*, 3rd Edition, by Craig, London, 1912.

[3] Kirkham, *loc. cit.*

[4] Donaldson, *loc. cit.*

SENESCENCE

As age advances, in addition to the menopause changes which relate more especially to the cessation of the female generative functions, atrophic changes of one sort or another take place in both sexes throughout practically the entire system. The internal spongy structure of the bones is dissolved away, so that they are left with only a hard external shell and consequently become brittle. The teeth decay and drop out. The muscles shrink in volume, the actual fibres of which they are composed becoming smaller in size and fewer in number. The arterial walls lose their elasticity and undergo sclerosis, a characteristic which is so constant that it has given rise to the well-known dictum that "a man is as old as his arteries." The tendons and ligaments also become calcified, and there is a consequent shrinkage of stature. The size of the liver and other viscera undergoes diminution, but the kidney and heart retain their size; in fact the heart is usually slightly enlarged in old age, but this apparent hypertrophy is not associated with an accession of power but with an increased feebleness, and the pulse, in order to compensate for the weakness of the enlarged heart, beats more quickly, the normal rate of seventy-two beats per minute rising to seventy-nine or eighty. The rate of respiration also rises slightly, and the vital capacity of the lungs diminishes. Moreover, the amount of carbon dioxide and urine which are excreted becomes less. The pigment in the hair undergoes absorption, the hair turning grey or white. The adipose tissue beneath the skin disappears, especially in advanced old age, but fatty degeneration of muscle or glandular tissue is not infrequent. In the male sex the prostate gland undergoes atrophy, or in some cases a pathological hypertrophy, which is said to be the cause of frequent penile erections.

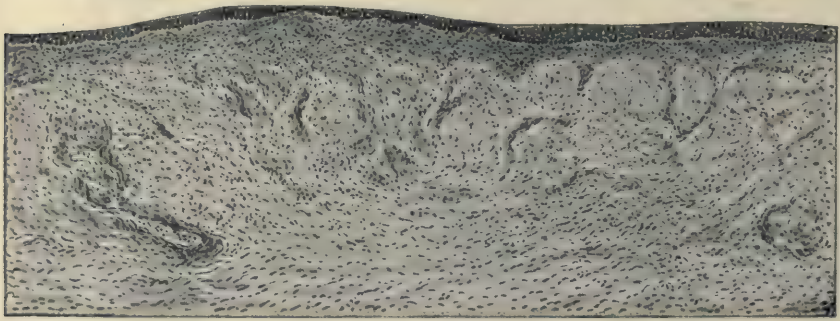

FIG. 185.—Section through vaginal mucous membrane of woman of sixty-one. (From Sellheim.)

It has been shown also that the brain decreases in size in old age. The shrinkage begins soon after maturity, and then continues almost steadily to the very end of life.[1] Handmann[2] has published the following statistical results, which are based on measurements carried out at the Pathological Institute at Leipzig:—

	Weight of Brain.	
Age.	*Male.*	*Female.*
4-6	1215 grams.	1194 grams.
7-14	1376 „	1229 „
15-49	1372 „	1249 „
50-84	1332 „	1196 „

The decrease in brain weight is accompanied by a diminution in the thickness of the cortex and in the number of tangential fibres present in it. These changes are associated on the psychical side with a gradual mental failure—loss of memory, decrease in the power of original thought and in the assimilation of new ideas, and general decline of mental activity. Moreover, the reaction time is lengthened, the sense organs lose their delicacy, and in the eye the power of accommodation is largely lost.

The minute cellular changes in the tissues are no less pronounced. These also are in the direction of atrophy. There is a general shrinkage in the protoplasm of the cells, but especially in the nuclei, so that the relative amount of cytoplasmic to nuclear substance becomes increased in old age. The nucleoli also tend to disappear. Hodge[3] has made a comparison of the changes in the cells of the first cervical ganglion with the following result:—

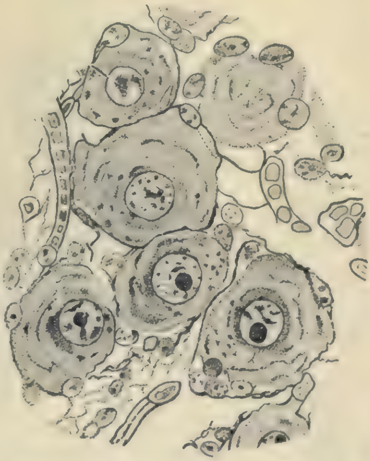

FIG. 186.—Group of nerve-cells from the first cervical ganglion of a child at birth. (After Hodge, from Minot's *Age, Growth, and Death*, G. S. Putnam & Sons, and John Murray.)

	Volume of Nucleus.	*Nucleoli observable in Nucleus.*
At birth	100 per cent.	In 53 per cent.
At 92 years	64·2 „	„ 5 „

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[1] Minot, *loc. cit.*

[2] Handmann, "Über das Hirngewicht des Menschen," *Arch. f. Anat. u. Phys.*, Anat. Abth., 1906.

[3] Hodge, "Die Nervenzelle bei der Geburt und beim Tode an Alterschwäche," *Anat. Anz.*, vol. ix., 1894.

Thus the nucleoli are often apparently quite absent in extreme old age. The nuclei, besides becoming smaller, grow irregular in shape, and in the cytoplasm there is a deposition of pigment granules.

Senescence in men is said to commence at about the age of fifty,[1] but it is obvious that no definite limit can be assigned to the period, since in some of the organs changes which are in their nature degenerative begin quite early in life.

Spermatozoa continue to be produced even in quite advanced old age, and instances have been recorded of men of 94, 96, and even 103 in whose semen active sperms were found.[2] There can be no doubt, however, that the spermatozoa are produced in far less abundance in old age.

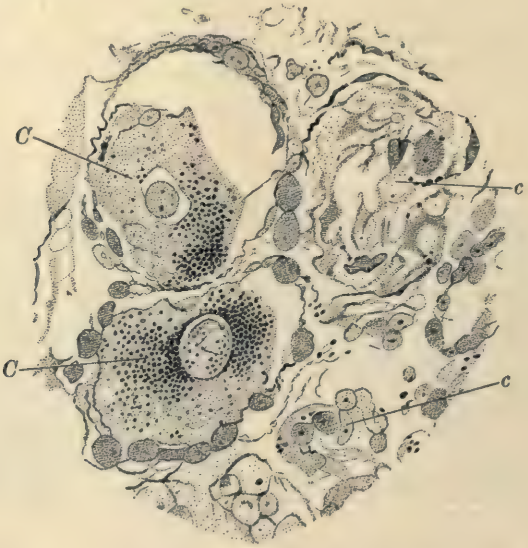

FIG. 187.—Group of nerve-cells from the first cervical ganglion of a man of ninety-two. (After Hodge, from Minot's *Age, Growth, and Death*, G. S. Putnam & Sons, and John Murray.)

C, C, Cells still intact, but shrunken and loaded with pigment; *c*, *c*, cells which have disintegrated.

In women the period of senescence is usually reckoned from the menopause.[3]

It is difficult to form any accurate comparison between the phases of life of men and those of animals, partly because so little is known regarding the conditions of natural senescence and death in animals. Smith[1] remarks that few horses live long enough to show much sign of arterial degeneration. The work they perform is the chief cause of their rapid decay, for their legs wear out before their bodies. But, apart from this, degenerative changes in the teeth, and more particularly the wearing away of the molars, prevent many horses from reaching a real old age. Blaine[2] has drawn the following comparison between the age of a horse and that of a man: "The first five years of a horse may be considered as equivalent to the first twenty years of a man; thus, a horse of five years may be *comparatively* considered as old as a man of twenty; a horse of ten years as a man of forty; a horse of fifteen as a man of fifty; a horse of twenty as a man of sixty; of twenty-five as a man of seventy; of thirty as a man of eighty; and of thirty-five as a man of ninety."

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[1] Lee, *loc. cit.*

[2] Cooper, *The Sexual Disabilities of Man, etc.*, London, 1908.

[3] For further information bearing on the subject see Stanley Hall, *Senescence*, New York, 1922.

THE DURATION OF LIFE AND THE CAUSE OF DEATH

Weismann, in a famous essay on the duration of life,[3] and Metchnikoff in his book of optimistic studies,[4] have dealt at some length, but from different standpoints, with the factors which determine longevity in the animal kingdom. That the duration of life in the various races of animals is very variable, and that, whereas some species are remarkably long-lived, others die after a relatively brief existence, are facts that are known to all. Both Weismann and Metchnikoff cite numerous instances of longevity among animals, some of the more extreme of which may be mentioned here.

A sea-anemone belonging to the species *Actinia mesembryanthemum* is known to have lived for sixty-six years, and to have produced young, though in smaller numbers than formerly, at the age of fifty-eight. Another sea-anemone of the species *Sagartia troglodytes* lived to be fifty years old.[5] Certain marine Mollusca are said to live for as many as a hundred years. Among insects there is an extraordinary variability in the duration of life, some living in a condition of maturity for only a few days or even hours, while others (certain Hemiptera) are believed to survive for as many as seventeen years. Moreover, the duration of life is sometimes very different in the two sexes, the queen ant being known to live for several years (in one case for fifteen years), whereas the male ant survives for only a few weeks.

[1] Smith, *loc. cit.*

[2] Blaine, *Encyclopædia of Rural Sports*, London, 1858.

[3] Weismann, "The Duration of Life," English Translation, in *Essays upon Heredity, etc.*, 2nd Edition, Oxford, 1891.

[4] Metchnikoff, *The Prolongation of Life*, English Translation, London, 1907.

[5] Ashworth and Annandale, "On Some Aged Specimens of *Sagartia*," *Proc. Roy. Soc. Edin.*, vol. xxv., 1904.

Among fish, pike and carp are usually said to attain to great ages and even to live for centuries, but there are few accurate data.

Among reptiles, crocodiles and tortoises are known to have long lives, a tortoise from the Galapagos Islands being stated to have lived for 175 years.

The length of life in birds has been discussed by Gurney,[1] who cites several examples of great longevity, but the more usual duration of life is from fifteen to twenty years. Canaries are stated to have attained to twenty years of age, a herring gull to forty-four, an imperial eagle to fifty-six, a heron to sixty, an eagle owl to sixty-eight, a raven to sixty-nine, a swan to seventy, and a goose to eighty. Hobday[2] has recently described a pair of ring-doves which lived to be twenty-one, and then did not die a natural death. Metchnikoff records a case of a parrot which lived for eighty-two years.

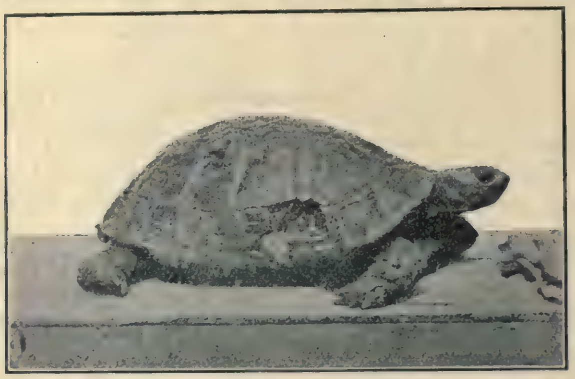

Fig. 188.—Land tortoise (*Testudo mauritanica*), aged at least eighty-six, belonging to M. Élie Metchnikoff.

(From Metchnikoff's *The Prolongation of Life*, by permission of Mr W. Heinemann.)

Mammals on the average appear to have considerably shorter lives than birds. According to Weismann, whales live for some hundreds of years, but it is difficult to see how this can be more than an assumption. There can be little doubt that the great age assigned by some of the older writers to elephants is mythical, and probably 150 years is almost the maximum ever attained. Horses in rare cases have reached forty years, cattle somewhat over thirty, and sheep over twenty years. A dog is said to have lived for thirty-four years, but twenty is usually regarded as a great age for this animal. Cats have been known to live to be twenty-one and even twenty-three, but no greater ages appear to have been recorded. The white rat may live forty months, or even longer, but the average age appears to be about thirty-four months.[1] The white mouse is stated to have a normal life of two years, and this whether it has bred or not, but females are slightly shorter lived than males.[2]

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[1] Gurney, "On the Comparative Ages to which Birds Live," *Ibis*, vol. v., 1899.

[2] Hobday, "An Instance of Longevity in Ring-Doves," *Vet. Jour.*, vol. lxxvi., 1920.

For man the traditional duration of life is seventy, but, as every one knows, this age is very often much exceeded. Women on the average live to be somewhat older than men.

Many instances are on record of extraordinary longevity, but perhaps the most trustworthy is the famous case of Thomas Parr, described by Harvey in the *Philosophical Transactions* of the Royal Society.[4] His death is said to have been due to the change in his mode of life, resulting from his migration from Shropshire to London, "where he fed high and drunk plentifully of the best wines." "He died after he had outlived nine princes, in the tenth year of the tenth of them, at the age of one hundred and fifty-two years and nine months."[5]

FIG. 189.—Lonk sheep, aged eighteen years, with her last lamb. This sheep, which belonged to Mr. William Peel of Knowlemere Manor, Clitheroe, lived to be twenty-one years. It had thirty-five lambs, nine of which were triplets.[3]

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[1] Donaldson, *loc. cit.*

[2] Kirkham, *loc. cit.*

[3] I am indebted to my friend Mr. W. Ralph Peel, of Trinity College, Cambridge, for this photograph (taken by his sister, Miss Peel), and for the information which accompanied it.

[4] Harvey, "Anatomical Account of Thomas Parr," *Phil. Trans.*, vol. iii., 1700. A portrait of Parr painted by van Dyck may be seen in the Royal Gallery at Dresden.

[5] For much further information about old age, longevity, etc., in man, see Luciani, *Human Physiology*, vol. v., English Edition, London, 1921. See also Pearl, "On the Mean Age at Death of Centenarians," *Proc. Nat. Acad. Sci.*, vol. v., 1919.

As to what factors determine the average duration of life in different species is a problem about which there has been much speculation. Weismann has elaborated a theory which asserts that living matter was originally immortal, mortality first arising in correlation with cellular differentiation. On this view the Protozoa are potentially immortal,[1] natural death occurring only among multicellular organisms. The protoplasm of the latter is shown to be of two kinds—germplasm, which is capable of propagating itself indefinitely under suitable conditions like the protoplasm of unicellular organisms, and somatoplasm, which composes the rest of the body and is subject to natural death. The life of the somatic cells was at first limited to one generation, but afterwards in the higher Metazoa was extended to many generations, and the life of the organism was lengthened to a corresponding degree. Such a restriction went on hand in hand with a differentiation of the parts of the organism into somatic and reproductive cells, in accordance with the principle of the physiological division of labour, and this process of differentiation was controlled by natural selection. "Death itself," says Weismann,[2] "and the longer or shorter duration of life both depend entirely on adaptation. Death is not an essential attribute of living matter; it is neither necessarily associated with reproduction, nor a necessary consequence of it." According to this theory, therefore, the phenomena of senescence and death, as exhibited by all the cells of the body with the exception of the germ-cells, are secondary properties which have been preserved in multicellular organisms by natural selection, because they are of direct advantage in the propagation of the species. An indefinite prolongation of the life of the organism after the age of reproduction had been passed would be of no value or utility to the race, but rather a disadvantage, since it would tend to retard the evolution of more perfectly adapted forms of life. Furthermore, according to Weismann, longevity, although depending ultimately upon the physiological properties of the cells, is capable of adaptation to the conditions of existence, and consequently is influenced by natural selection just in the same way as other specific characters are.

Perhaps the most cogent criticism of Weismann's doctrine of immortality is that of Verworn, who writes as follows: "The conception of living substance as immortal will be accepted by scarcely anyone who bears in mind the characteristic peculiarity of living substance, viz., that it continually decomposes, or, in other words, dies. There is no living substance that, so long as it is living at all, is not continually decomposing in some parts, while being regenerated in others. No living molecule is spared this decomposition. The latter, however, does not seize upon all molecules at the same time; while one is decomposing, another is being constructed, and so on. One living particle affords the conditions for the origin of another or several others, but itself dies. The particles newly formed in turn give rise to others and, likewise, die. In this manner living substance is continually dying, without life itself becoming extinct."[1] From this standpoint, therefore, there can be no question of any kind of living substance being truly immortal. The whole conception of a possible immortality arises from a confusion of ideas.

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[1] This question, about which there has been much controversy, is referred to in Chapter VI. (pp. 220-224).

[2] Weismann, "Life and Death," *Essays*, vol. i., 2nd Edition, Oxford, 1891.

Minot,[2] on the other hand, has elaborated a theory of senescence which may be regarded as an extension of that of Weismann. Like the latter, he seems to assume that death is not a universal accompaniment of life, and that natural death has been acquired in the course of evolutionary development. He proceeds to define senescence as an increase in the differentiation of the protoplasm. During the early periods of life the young material is produced, and the protoplasm is undifferentiated. During the later stages of existence cell differentiation goes on, and the organism gradually becomes old. When the cells acquire the faculty of passing beyond the simple stage to the more complete organisation, they lose something of their vitality, of their power of growth, and of their possibilities of perpetuation. Just as senescence depends upon the increase and differentiation of the cytoplasm, so, conversely, rejuvenation depends upon the increase of the nuclear material; and consequently the alternation of the two phases of the life cycle (the early brief one when the young material is formed, and the later prolonged one when the process of differentiation is going on) is due to an alternation in the proportions of nucleus and protoplasm. In criticism of this theory, it may be urged that it is in reality nothing more than a descriptive account of a general type of cellular change, and that it provides no sort of explanation as to why this type of change occurs, nor how it is that differentiation is apparently correlated with a reduction of vitality leading eventually to death.

Robertson and Ray[3] have recently adduced evidence for the view that the potential longevity of any given individual is determined by the relative velocities of anabolism in the cellular and sclerou tissues respectively. This hypothesis is based on a series of experimental studies on the growth of the mouse under different conditions (see p. 712).

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[1] Verworn, *General Physiology*, Lee's Translation from the second German Edition, London, 1899.

[2] Minot, *loc. cit.* For the views of Steinach, etc., on the interstitial gland, see p. 327.

[3] Robertson and Ray, *loc. cit.*

Metchnikoff has laid great stress on the idea that natural death is a rare phenomenon, at least among the higher animals. That death with man is frequently, if not generally, caused by disease or accident is a fact about which there can be no disagreement, and Karl Pearson[1] has worked out statistically the chances of death occurring in the different phases of human life. "We have five ages of man," he says, "corresponding to the periods of infancy, childhood, youth, maturity or middle age, and senility or old age. In each of these periods we see a perfectly chance distribution of mortality centring at a given age and tacking off on either side according to a perfectly clear mathematical law." It was found also that the curve of mortality, as deduced from a study of the deaths per annum of a thousand persons born in the same year, "starts very high in infancy, falls to its least value at thirteen or fourteen years with only 236 deaths. It then slowly increases till it reaches a maximum in the seventy-second year of life, and falls more rapidly than it rose, till scarcely two isolated stragglers of the thousand reach ninety-one." It is clear, therefore, that death from old age is far from being the rule in the human species, but, according to Metchnikoff, it seldom occurs at all.[2]

This biologist found it impossible to accept the view that the high mortality observable between the ages of seventy and seventy-five indicates a natural limit to human life at about this period. Centenarians, he points out, are not really very rare, and he cites many cases of extreme old age, including that of Thomas Parr referred to above. Real old age, we are told, is associated with an instinct for death which is as natural as is the instinct for sleep. Metchnikoff, therefore, answers in an emphatic negative the question asked by Admetus in Euripides' "Alcestis," "Is it the same thing for an old man as for a young man to die?" The fact that the instinct for death seems so rarely to exist is regarded as evidence that true senility is a comparatively infrequent phenomenon.

According to Metchnikoff, senescence is not brought about simply as the result of arrest of the reproductive powers of the cells. The whitening of hair in old age is due to the destructive action of phagocytes which remove the pigment. Moreover, hairs become old and white without ceasing to grow. Metchnikoff believed also that atrophy of the brain is due to the destruction of the higher nerve-cells by neuronophags, and that there are many other devouring cells which are adrift in the tissues of aged men and animals and cause the destruction of other cells of the higher type. The testes, however, appear to have the power to resist these phagocytes, and with this power is correlated the fact that spermatozoa are often produced even in advanced old age. Metchnikoff's theory as to the cause of death is that it is due to the poisoning of the tissues and to the damage done by phagocytes to those parts of the body affected by the toxic action. He believed further that in man and certain of the animals this process of poisoning is brought about by fermentation set up by microbial action in the large intestine. The toxic substances produced by the intestinal fermentation were supposed to enter the system and poison it, the result being that the vitality of the tissues is lowered, so that they are less able to resist the action of devouring phagocytes. The presence of lactic acid in the intestine was believed to arrest the process of fermentation. Metchnikoff recommended, therefore, the regular drinking of sour milk as a means of destroying the microbes in the intestine in the hope of prolonging life.

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[1] Pearson, *The Chances of Death, etc.*, vol. i., London, 1897.

[2] Metchnikoff, *loc. cit.*; and *The Nature of Man*, Mitchell's Translation, London, 1903.

The term "Death" is employed in two separate senses; it may mean the death of the whole body, *i.e.* somatic death (this being the sense in which it is ordinarily used), or it may be applied to the death of the individual tissues, some of which remain alive for many hours after the body as a whole is said to be dead. The death of the body as a whole usually occurs suddenly. As Michael Foster says: "Were the animal frame not the complicated machine we have seen it to be, death might come as a simple and gradual dissolution, the 'sans everything' being the last stage of the successive loss of fundamental powers. As it is, however, death is always more or less violent; the machine comes to an end by reason of the disorder caused by the breaking down of one of its parts. Life ceases not because the molecular powers of the whole body slacken and are lost, but because a weakness in one or other part of the machinery throws its whole working out of gear."[1]

The synchronous disturbance of two or more of the bodily functions, such as is wont to occur in old age, may destroy that co-ordination of the various vital activities without which life cannot continue. The stoppage of the heart's beat is the ordinary criterion of death, and this is a true conception, because the cessation of the heart's movements implies the arrest of the circulation of the blood and the consequent starvation of the tissues of the body.

The tissues do not die simultaneously, for, as already described, some cells of the body are in process of disintegration through the whole of life. After somatic death, the cells which make up the nervous system usually die very rapidly. The same is true of the gland-cells; but the muscles may remain sensitive to external influences for many hours. In animals it has been shown that the heart itself after removal from the body, if kept under suitable conditions and perfused with an artificial fluid resembling blood-serum, may continue to live and undergo rhythmical contractions for a considerable time. In the process of death-stiffening, or *rigor mortis*, the muscles once more contract spontaneously, and not till this has happened is their life utterly extinguished. *Rigor mortis* is brought about by the coagulation of the muscle plasma within the cells. It begins at periods varying from half an hour to thirty hours after somatic death, and it continues for an average of about thirty hours. Certain cells may even live for some time after *rigor mortis* has passed. This is notably the case with the ciliated epithelial cells of the inner surface of the respiratory passages, and with the white corpuscles of the blood. Sooner or later, however, every part of the organism perishes, putrefactive changes set in, and the entire substance of the body passes once more to that "dust" out of which its vital activities enabled it to build itself up in the progress of individual life.

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[1] Foster, *Text-book of Physiology*, Part IV., 5th Edition, London, 1891.

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